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THE EXPERIMENTAL PRODUCTION AND PREVENTION OF DEGENERATION IN THE SPINAL CORD.

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IN 1926, E. Mellanby described before the Physiological Society experimental work in which degenerative changes of nerves in the spinal cord of dogs were produced and prevented under certain dietetic conditions [1]. Since then developments of this work, especially in relation to ergot, have been from time to time described in lectures before medical and scientific bodies [2 and 3].[1] The investigations have made but slow progress and even now the subject is in an elementary stage. The experimental procedure as at present used is prolonged and the unravelling of the factors involved has necessitated the examination and the elimination of many food elements. A sufficient number of facts have, however, come to light to warrant their description, and it is hoped that this publication will hasten the further elucidation of a physiological and pathological problem which may have a wide bearing on nervous disease in man. Some of the experimental symptoms and lesions produced in the dogs, and the manner in which these are produced and prevented, are so reminiscent of nervous ergotism, pellagra and lathyrism, found in man, especially in times of dietetic restriction, that the experiments seem certain to throw light on the ætiology of these human illnesses. Their significance may, however, be of wider interest, for demyelination of central nervous system fibres is a characteristic change, although it is found in such varied diseases as pernicious anæmia, tabes dorsalis, disseminated sclerosis, general paralysis, post-vaccinal encephalitis and

[1] In addition to the occasions referred to, the facts mentioned below, except those concerning the action of carotene, were described before the Manchester Medical Society, October, 1928, and also in a series of lectures given at University College, London, in May, 1929.

cancer. The experimental work may also have some bearing on the causation and control of these conditions. A discussion on its possible significance will be given at the end of the report.

Since Eijkman's classical work published in 1897 [4] in which he produced polyneuritis gallinarum by means of diet, it has been recognized that the structure and function of peripheral nerves are controlled by a specific dietetic ingredient, namely vitamin B_1. Eijkman's discovery formed the starting point of that fruitful field of study which embraces the group of pathological conditions known as "deficiency diseases," a group which includes scurvy, rickets, infantile tetany, dental hypoplasia and caries, periodontal disease (pyorrhœa alveolaris), pellagra and probably certain types of bacterial and worm infection. Of course there are, in some of these at least, other factors at work than the specific deficiency, but generally speaking, the other factors are harmless provided there is or has been no specific dietetic deficiency. Evidence will be given in this paper to show that demyelination of spinal cord fibres is yet another instance which illustrates, among other things, the importance of specific dietetic factors in physiological development and function.

Apart from the work of Orr and Rows [5] who studied spinal cord degeneration produced by bacteria and bacterial toxins, experimental investigation on this aspect of the central nervous system has not been very fruitful. In 1916, Hart, Miller and McCollum [6] described changes in the anterior horn cells of pigs' cords produced by means of dieting. The changes described by these authors included shrinkage of the motor cells especially those of the ventro-medial and ventro-lateral columns, crowding of Nissl's granules, the near obliteration of nucleus and nucleolus, and degeneration of the processes. No changes in the conducting fibres of the spinal cord were described. The authors decided they were dealing with a form of beri-beri, not, however, due to a deficiency of vitamin B, which was present in abundance in the wheat germ portion of the diet. Indeed the pathological condition was ascribed to a toxic action of the wheat germ. By supplementing the diet with alfalfa meal and meat scraps the cell changes were prevented. They ascribed the protective effects of these foodstuffs to a combined action of additional proteins, fat-soluble vitamin and a better salt mixture, but did not consider that any one of these substances could in itself afford protection. As far as I know, they did not follow up this work.

More recently an account of an investigation bearing closely on the

present work has been published by Hughes, Lienhardt and Aubel [7], in which is described the experimental production of degenerated fibres in the spinal cord and peripheral nerves of animals by means of diet. Young pigs were fed from the time of weaning on white corn, tankage and bone ash and in six to ten months developed blindness, inco-ordination and spasms. On post-mortem examination degenerative changes were found by these workers in the spinal cord and in the optic, sciatic and femoral nerves. The addition of cod-liver oil, butter fat, yellow corn and alfalfa leaf meal prevented or relieved the condition, and thus the preventive factor was probably vitamin A.

Finally, there remain for reference some interesting results obtained by Castle. For an account of this work I am indebted to Dr. Castle and for the privilege of seeing his unpublished manuscript. He fed a number of dogs on diets deficient respectively in vitamins B_1 (anti-neuritic) and B_2 (pellagra-preventing), and some with a combined deficiency of both vitamins. In all the animals deprived of the anti-neuritic vitamin he found post mortem a diffuse, irregular loss of myelin chiefly in the white matter of the cord and some in the cerebral cortex. In nine out of these fourteen animals slight lesions of the peripheral nerves were also found. Early changes were found post mortem in the nervous system of four dogs fed on the diet deficient in vitamin B_2, but in life the animals did not show any significant neurological symptoms. It is of interest to note that the nervous symptoms in the animals deprived of vitamin B_1 could always be improved within a few hours by the administration of a source rich in this substance. This particular observation of Castle's is reminiscent of the rapid results seen in avian beri-beri following the administration of vitamin B_1 and suggests that the problem here is a similar one to that of avian beri-beri rather than to that of combined system disease seen in human beings.

The history of the present investigation dates back to the time when experiments were made on puppies with the object of determining the ætiology of rickets (E. Mellanby) [8]. The rachitic animals often developed great weakness, especially noticeable in the hind legs; the weakness was sometimes associated with spasticity. At first it was thought that the muscular weakness was one of the manifestations of rickets and this idea was supported by the fact that substances, such as cod-liver oil and milk, which cured or prevented rickets cured or prevented the muscular weakness. At a later stage in the work (1923) it was noticed that some of the experimental animals developed severe inco-ordination when they attempted to walk, and it was this inco-ordinated

gait which led to the examination of the spinal cord by histological methods. It was soon realized that there was more in the problem than rickets, for although some rachitic animals showed degenerative changes in the spinal cord, others did not. Indeed, there was no definite relationship between the pathological changes in the bones and the nervous system. Throughout much of the original work on rickets, which led to the establishment of the anti-rachitic vitamin, there was no clear differentiation between the anti-rachitic vitamin (vitamin D) and vitamin A, and this fact, as will be seen later, resulted in confusion of the explanation of the nerve degeneration results. Indeed, it was

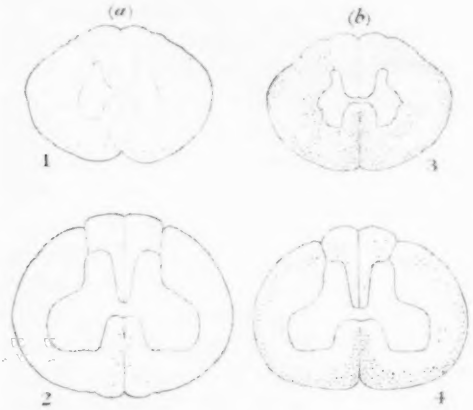

FIG. 1.—Drawings representing the distribution of degenerating nerve fibres as shown by the Marchi technique in the spinal cords of (*a*) and (*b*). (Experiment I.) Drawings 1 and 2 represent sections through the 2nd cervical and 6th cervical regions respectively of (*a*) (white flour). Drawings 3 and 4 are corresponding sections of (*b*) (white flour plus wheat germ). Note the greater amount of degeneration in the cord of (*b*), and also that the degenerating fibres are more scattered in the higher region.

only possible in this case, as in the problem of susceptibility to bacterial infection and its relation to diet, to begin to sort out the various experimental phenomena observed when the differentiation between vitamins A and D was finally established.

Although it soon became obvious that a fat-soluble vitamin played a part in preventing the cord degeneration, attention was first focused on the positive aspect of the phenomenon, for it seemed probable that just as cereals had an interfering action on bone calcification [9] so also they would under certain conditions exert a toxic effect on the nervous system. Difficulties were, however, encountered in the variable results

obtained in different litters of puppies. In some litters the spinal cord degeneration could be easily produced when the diet contained much cereal and was deficient in fat-soluble vitamins. On the other hand, some litters were refractory and showed no cord changes during the experimental period. In those litters giving a positive result, although the addition of wheat germ usually made the cord changes more extensive, yet those eating white flour alone as the cereal part of the diet sometimes developed fairly marked degenerative changes in the spinal cord.

Some of these discrepancies are now easier to understand in the light of further experimental work.

It may be well before describing later developments to illustrate some of the positive results obtained with diets containing white flour, oatmeal and wheat embryo as cereals because it is important that it should be recognized that the pathological changes can often be produced by natural foodstuffs.

EXPERIMENT I.

Production of Spinal Cord Degeneration by Diets which include White Flour and Wheat Germ.

Age beginning: 10 weeks.

Duration of experiment: About 4 months.

Basal diet: Separated milk powder, 20-30 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5-5·0 grm.: orange juice, 3-6 c.c.: sodium chloride, 1-2 grm.

(*a*) had white flour.

(*b*) had 60 per cent. white flour, 40 per cent. wheat germ.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	—	Little degeneration	Active during much of experiment. Fairly steady on legs but weak
(*b*)	Wheat germ	Much degeneration	Very inco-ordinate. Puts legs down slowly and unsteadily: later paralysed

The rate of growth of the two animals was similar.

The degenerative changes of the cords of these animals when stained by Marchi's method are represented in fig. 1.

In this experiment, degeneration developed in the spinal cords of both animals, but in (*b*), with wheat germ added to the diet, it is more extensive.

Another experiment giving similar results may be quoted.

Experiment II.

Production of Spinal Cord Degeneration by Diets which include Oatmeal and Wheat Germ.

Age beginning: 7 weeks.

Duration of experiment: About 3 months.

Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 3 grm.

(*a*) had oatmeal.

(*b*) had 80 per cent. oatmeal, 20 per cent. wheat germ.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	—	Little degeneration	Nearly normal .. .. ..
(*b*)	Wheat germ	Fair amount of degeneration especially in Cii, in anterior, antero-lateral, and direct cerebellar tracts	Hind legs stiff; later dragged hind legs when walking; later still inco-ordinate

The rate of growth of the two animals was good and comparable during the greater part of the experiment, but towards the end both lost weight, especially (*b*).

These two experiments illustrate the fact that degenerative changes in the cord can be produced in young dogs by diets rich in cereals when the fat-soluble vitamin intake is deficient.

In the following experiments it is demonstrated that the degenerative changes can be prevented by adding to the food a source of fat-soluble vitamins. In the first of these experiments olive oil and butter are compared; in the second, butter fat is used with its fat-soluble vitamin content respectively intact and destroyed by heat and oxidation.

Experiment III.

Production of Spinal Cord Degeneration by Diets which include Bread, Wheat Germ and Varying Quantities of Fat-soluble Vitamins.

Age beginning: 7 weeks.

Duration of experiment: About 2 months.

Basal diet: Bread (80 per cent.) and wheat germ (20 per cent.); separated milk powder, 20-25 grm.; lean meat, 10-20 grm.; yeast, 3-5 grm.; orange juice, 3 c.c.; salt, 1 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	Olive oil, 10 c.c.	Much degeneration	Could not walk straight; had fits occasionally. Inco-ordinate, and finally paralysed. Eyes ulcerated
(*b*)	Butter, 10 grm.	No degeneration	Normal

Both animals grew well for the greater part of the experiment.

Experiment IV.

Production of Spinal Cord Degeneration by Diets which include Bread, Wheat Germ, Treated and Untreated Butter Fat.

Age beginning: 8 weeks.

Duration of experiment: About 4 months.

Basal diet: Bread (80 per cent.) and wheat germ (20 per cent.); separated milk powder, 20 grm.; lean meat, 20-10 grm.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt 1 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	Olive oil ..	Much degeneration	Looked dazed; abnormal gait; later paralysed
(*b*)	Butter fat ..	No degeneration	Nearly normal
(*c*)	Butter fat heated and oxygenated 12 hours	Much degeneration	Looked dazed; inco-ordinate; back legs weak: later paralysed

The rate of growth of the three puppies was fairly comparable during the greater part of the experimental period.

Although under the experimental conditions described it is generally possible to obtain the degeneration with cereals, this is not always the case, and the variability made it necessary to seek other means of pursuing the investigation.

It was thought possible that the varying results might depend not only on the early history of the puppies but also on variations in the samples of cereals and especially of the wheat germ. Now the cord degenerations, and to some extent the clinical symptoms, called to mind the pathological conditions of the nervous system associated with human convulsive ergotism. It seemed possible, therefore, that some batches of the wheat germ were ergotized, i.e., infected with the fungus *Claviceps purpurea*, although, since white flour was sometimes associated with cord changes, this explanation was not very likely. Microscopic examination of the wheat germ also gave no support to this supposition. Attempts were, nevertheless, made to produce cord degeneration by adding ergot of rye to the diets of some animals. It seemed indeed probable that if, by the use of ergot, a more certain method of producing demyelination of the spinal cord could be obtained, the problem would be more amenable to study and possibly lead to a clearer understanding of the difficulties.

Reference to the literature dealing with experimental nervous

ergotism in animals did not give much prospect of success. Tuczek [10] not only had much experience of convulsive ergotism in man but also made many attempts to produce cord degeneration in animals by adding ergot to the diet. He described the degenerative changes in the cords of patients deceased of nervous ergotism, but never succeeded in producing similar changes in the cords of animals, although he refers to the paralysis, stiffness, weakness and staggering gait produced in dogs which had received 4 to 6 grm. of ergot daily. Writing in 1882, at a time when convulsive ergotism in Germany was an important practical problem, he says of animal experiments, "Positive Sectionsergebnisse in Centralnervensystem bei Ergotismus finde ich in der Literatur nirgends!" Of course, the technical methods used for preparing nervous tissue for microscopic examination were cruder in those days and this may account for the negative results. Whether spinal degeneration in experimental animals such as is described below has been produced by ergot and demonstrated since Tuczek's time, I have not been able to discover.

The following experiments show that nervous ergotism can be induced in dogs under certain dietetic conditions, and that slight alterations in the diet of a specific nature completely prevent the cord degenerative changes even when the same or larger amounts of ergot are eaten.

Spinal Cord Degeneration produced by Ergot of Rye.

In the early experiments, ergot in small quantities (2 to 5 grm. daily) was added to diets deficient in fat-soluble vitamins, but otherwise, so far as was known, complete, and given to puppies of the same litter. Previous experiments in which the cord changes had developed when cereals formed a large part of the diet suggested that the absence of fat-soluble vitamins would also play an important rôle in controlling any influence on the nervous system that ergot might exert.

Before describing the experimental results it may be well to say that, although it is usually an easy matter to feed puppies on diets deficient in fat-soluble vitamins for some months, it is by no means easy to get them to take ergot under these conditions. They may eat up their food containing the ergot for a few days or weeks and then either refuse it or eat their ration incompletely. To meet this situation different devices are necessary varying with the animal in question. Sometimes the ergot is mixed with a small portion of the food and given as a bolus after some of the food has been eaten, sometimes the amount of ergot is reduced,

and sometimes it is necessary to suspend giving the ergot for at least a few days. In all cases care and discretion are needed, especially as it is advisable that the animals should not lose weight before the symptoms of nervous ergotism are produced.

The following experiment illustrates the intensification of cord degenerative changes when ergot is added to a diet rich in cereal and deficient in fat-soluble vitamins.

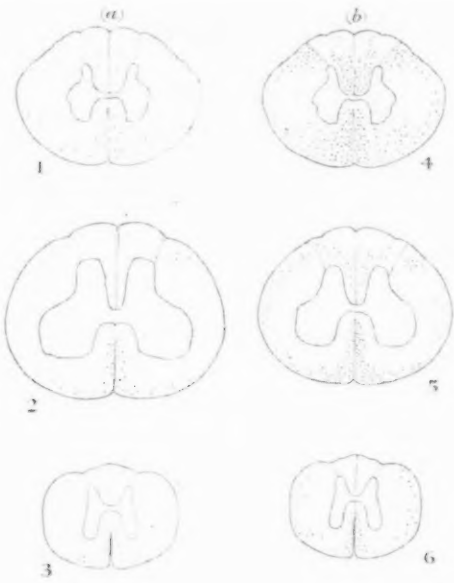

FIG. 2.—Drawings representing the distribution of degenerating nerve fibres as shown by the Marchi technique in the spinal cords of (*a*) and (*b*). (Experiment V.) Drawings 1, 2 and 3 represent sections through the 2nd cervical, 6th cervical and 11th dorsal regions respectively of (*a*) (control diet). Drawings, 4, 5 and 6 represent corresponding sections of (*b*) (ergot). Note the greater amount of degeneration in the cord of (*b*) (ergot), and that there is comparatively little degeneration in the dorsal region.

EXPERIMENT V.

The Production of Degeneration by Ergot.

Age beginning: 9 weeks.

Duration of experiment: About 2 months.

Basal diet: Bread; separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 grm.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt 1 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Some clinical notes
(*a*)	—	A little degeneration *Ci. A little* degeneration in anterior, antero-lateral columns. A few degenerated fibres in Burdach *Cvi. A little* in anterior and antero-lateral columns. Very little in direct cerebellar, none in Burdach *Dxii. Little* degeneration in anterior column	Fairly active but rather unsteady out of cage
(*b*)	Ergot, 2 g. ..	Much degeneration *Ci. Much* degeneration in anterior and antero-lateral columns, direct cerebellar and Burdach *Cvi. Much* degeneration in anterior column, some antero-lateral and direct cerebellar; little in Burdach *Dxii. Little* degeneration, most in anterior columns	Not very active, and decidedly inco-ordinate

Puppy (*b*) grew steadily throughout the experimental period; (*a*) grew well at first but later lost some weight. The cord changes in these two animals are represented by the drawings of fig. 2.

It will be seen in this experiment that while there is some degeneration in the cord of the control animal, the addition of ergot to the diet has greatly intensified the pathological changes.

In the following experiment not only is the effect of adding ergot examined (*b*), but the stability of the toxic factor in ergot is tested by (1) heating it for eighteen hours at 120° C. (*c*), and (2) boiling it for one hour with 1 per cent. hydrochloric acid (*d*).

Experiment VI.

The Production of Degeneration by Treated and Untreated Ergot.

Age beginning: 8 weeks.

Duration of experiment: About 4½ months.

Basal diet: Bread, 180 grm.; separated milk powder, 20 grm.; lean meat, 20 grm.; peanut oil, 10 c.c.: orange juice, 3 c.c.: dried yeast, 2 grm.; sodium chloride, 1 grm.

(*a*) had basal diet only.

(*b*) had in addition untreated ergot (2·5 grm. daily).

(*c*) ,, ,, ,, ergot treated 18 hours at 120° C. (2·5 grm. daily).

(*d*) ,, ,, ,, ergot boiled with 1 per cent. HCl for 1 hour (2·5 grm. daily).

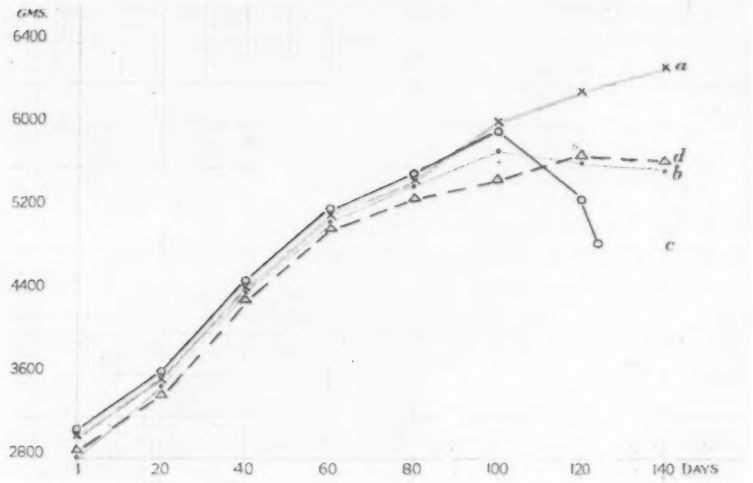

FIG 3.—Weight curve for Experiment VI. *See also* Fig. 4.

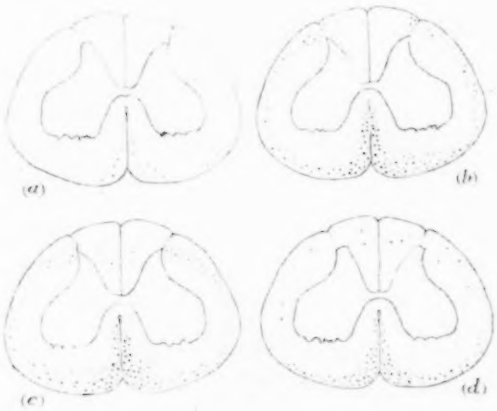

FIG. 4.—Drawings representing the distribution of degenerating nerve fibres as shown by the Marchi technique in the spinal cords at the level of the 6th cervical in dogs (*a*), (*b*), (*c*) and (*d*) of Experiment VI. (*a*) Control; (*b*) ergot; (*c*) heated ergot; (*d*) ergot boiled with dilute acid. Note the increased degeneration produced by ergot whether untreated, heated, or after being boiled with acid. In the latter case the increase is not so great.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(a)	—	Little degeneration	Slightly inco-ordinate
(b)	Untreated ergot	Much degeneration	Inco-ordinate. Dazed appearance; several fits
(c)	Heated ergot	Much degeneration	Inco-ordinate. Very weak and ultimately paralysed. Head movements uncontrolled
(d)	Ergot boiled in weak acid	Much degeneration, but rather less than (b) and (c)	More active than (c), but inco-ordinate; dazed appearance

For rate of growth, see fig. 3; for distribution of degeneration, see fig. 4.

This experiment shows not only the increase in cord degeneration produced by ergot, but that the neuro-toxin in ergot is stable to heat and, to a less extent, to boiling with 1 per cent. hydrochloric acid for one hour.

Similar experiments were made on many litters of puppies with the same results,[1] so that it now appeared that a sufficiently reliable means of producing spinal cord degeneration was at hand to allow a more extended study of the problem.

The first point which required investigation was to see whether the cord changes produced by ergot could be prevented by fat-soluble vitamins in the food, for, as mentioned above, demyelination had never been seen in the cords of animals when the diet included cod-liver oil, egg yolk and cabbage, even if the diet was composed largely of cereals.

At this stage of the investigation the method of preparation of vitamin D from ergosterol by irradiation with the mercury vapour lamp had just been announced by Rosenheim and Webster [11], and Windaus and Hess [12], so that it was possible to decide whether vitamin D was the factor in the fat-soluble vitamins which prevented nerve degeneration.

Experiment VII.

Degenerative Changes produced in the Presence of Vitamin D.

Age beginning: 8 weeks.

Duration of experiment: About 7 months.

Basal diet: Bread, 100-160 grm.: separated milk powder, 20 grm.: lean meat, 20 grm.: dried yeast, 2·5 grm.: orange juice, 3 c.c.: salt, 1 grm.

Each animal also received on the average 3 grm. ergot daily.

[1] Since this was written, failure to produce the cord changes with ergot has been experienced in one litter of puppies. Although it is the only exception out of about forty experiments, this negative result may be of significance and may indicate that some unknown factor or factors have still to be elucidated.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	Olive oil, 10 c.c.	Much degeneration	Head position abnormal. Incoordinate. Discharge from eyes: later ulcer on one eye
(*b*)	Cod-liver oil, 10 c.c.	No degeneration	Normal
(*c*)	Irradiated ergosterol (Vitamin D)	Much degeneration: slightly less than (*a*)	Head position abnormal. Incoordinate. Discharge of pus from eyes

Advanced degeneration, as shown by Weigert's method of preparation, is seen in both (*a*) and (*c*).

This experiment makes it clear that (1) cod-liver oil prevents the neuro-toxic effect of ergot; (2) vitamin D is not the preventive agent.

A casual observation made during this and similar experiments also confirmed the ineffectiveness of vitamin D as a protective agent against ergot. It was noticed that when dogs received ergot, even when eating a diet deficient in fat-soluble vitamins, they did not develop the same intensity of rickets as the animals not getting ergot. It appeared, in other words, that ergot itself contained vitamin D, and so exerted an antirachitic action. This point was followed up, and ergot was shown to contain an appreciable amount of vitamin D (Mellanby, Surie and Harrison [13]), a discovery of interesting significance since, as will be remembered, Tanret [14] first isolated ergosterol, the parent substance of vitamin D, from ergot in 1889. Although ergosterol is very widely distributed in nature, it is rare to find any of it in the activated (vitamin D) form.

Now, since ergot produces spinal cord degeneration, and since it also contains vitamin D as a normal constituent, it did not seem likely that this vitamin in quantities sufficient to prevent rickets would inhibit the toxic action of ergot, a result which has been confirmed in Experiment VII. Since vitamins A and D are both present in cod-liver oil, which has been found to be preventive, it seemed fairly certain that vitamin A would prove to be the protective substance. In the following experiment, different sources of vitamin A were added to the diets in addition to ergot and the effect on the spinal cord studied. It may be stated that the beneficial effects of adding these sources of vitamin A were at once apparent in the general condition of the animals. The difficulty of feeding the ergotized diets greatly diminished, and the animals remained active and healthy looking throughout the experimental period.

Experiment VIII.

Degeneration Changes resulting from Ergot prevented by Sources of Vitamin A.

Age beginning: 8 weeks.

Duration of experiment: About 4½ months.

Basal diet: Bread; separated milk powder, 20 grm.; lean meat, 20 grm.; peanut oil, 10 c.c.; orange juice, 3 c.c.; dried yeast, 2 grm.; sodium chloride, 1 grm.

In addition all had on the average 2·5 grm. ergot daily.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Some clinical notes
(*a*)	—	Much degeneration	Inco-ordinate. Several fits; dazed appearance
(*b*)	Butter, 10 g., replacing peanut oil;	No degeneration	Active
(*c*)	Mammalian liver oil (vitamin A), 1 c.c.	No degeneration	Active
(*d*)	Cabbage boiled 30 min., 30-50 grm.	No degeneration	Active, but nervous and jumpy
(*e*)	1 egg yolk	No degeneration	Very active

The weight curves of these animals during the experimental period are shown in fig. 5.

Inference from these results :—

(1) Foods rich in vitamin A prevent the ergot from producing spinal cord degeneration.

(2) With vitamin A in the diet, the animals remain active, eat their food well, develop no nervous symptoms and remain in good health.

It may be added that the animals whose diet included vitamin A often had more ergot than other members of the litter because on diets deficient in vitamin A the ergot had more frequently to be omitted from the daily ration.

Rye Germ and Degenerative Changes in the Cord.

Ergot of rye develops as the result of the growth of a fungus, *Claviceps purpurea*, in the embryo of rye. The embryo under these conditions becomes bigger and is ultimately filled with mycelia of the fungus. It was of interest therefore to see whether rye germ

itself, free from the fungus, had any action on the spinal cord. It may be noted that, after ergot of rye was found to contain vitamin D (Mellanby, Surie and Harrison) [13], it was discovered that the rye embryo itself also contained some of this vitamin, although in smaller quantities than ergot. In other words, the mycelial invasion of the rye embryo did not produce *de novo* vitamin D but only exaggerated the development of a vitamin originally present in the rye germ. It

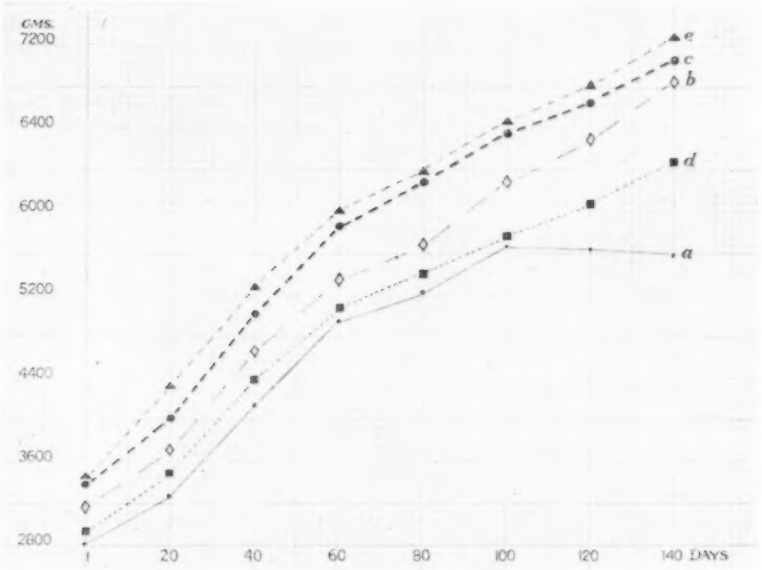

FIG. 5.—Weight curve for Experiment VIII.

seemed likely, especially in view of the earlier experiments with wheat germ, that rye germ would also afford evidence of containing the agent abundantly present in ergot of rye which hastens the cord degenerative changes. If this proved to be the case, it would show that the ergotizing of the rye embryo only results in the production of increased amounts of a toxic agent originally present in the rye germ itself. Experiments carried out to test the action of rye germ on the spinal cord proved that this substance does indeed contain the nerve toxin. The following series of tests made on a litter of puppies illustrates the point.

Experiment IX.

The Production of Cord Degeneration by Rye Germ.

Age beginning: 6 weeks.

Duration of experiment: About 5 months.

Basal diet: white flour; separated milk powder, 25 grm.; lean meat, 20 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; sodium chloride, 2·4 grm.

(*a*) had in addition petrol ether extract of rye germ equivalent to 20 per cent. of white flour.

(*b*) had basal diet only.

(*c*) had in addition rye germ replacing 20 per cent. of white flour.

(*d*) ,, ,, rye germ heated 36 hours at 120° C., replacing 20 per cent. of white flour.

(*e*) ,, ,, rye germ replacing 20 per cent. of white flour, and 20-50 grm. cabbage boiled ½ hour.

(*f*) ,, ,, rye germ extracted with petrol ether, replacing 20 per cent. of white flour.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Condition as regards rickets	Some clinical notes
(*a*)	Extract of rye germ	Some degeneration	Some rickets	Not normal but ran fairly well
(*b*)	—	Some degeneration	Bad rickets	Slightly inco-ordinate; paralysis in hind legs, from which recovered later
(*c*)	Rye germ	Much degeneration	Some rickets	Hind legs stiff, gait difficult. Head movements abnormal
(*d*)	Heated rye germ	Much degeneration	Rickets ..	Hind legs stiff, abnormal gait. Head movements abnormal
(*e*)	Boiled cabbage	No degeneration ..	Rickets ..	Ran fairly well. No inco-ordination
(*f*)	Extracted rye germ	Very much degeneration (also in Goll's column)	Very bad rickets	Gait abnormal; later hind legs paralysed

The degenerative changes in the cords of these animals are represented in fig. 7, and the changes in weight during the experimental period in fig. 6.

These experiments show that:—

(1) Rye germ contains an agent producing spinal cord degeneration, but probably to a less degree than ergot of rye, since much more rye germ was eaten in these experiments than ergot in similar experiments.

(2) This action of rye germ, like that of ergot, is inhibited by cabbage.

(3) Heating the rye germ for thirty-six hours at 120° C. has not destroyed the substance responsible for this action.

(4) The active agent in rye germ is not removed by petrol ether.

(5) There is no relationship between the amount of cord degeneration and rickets.

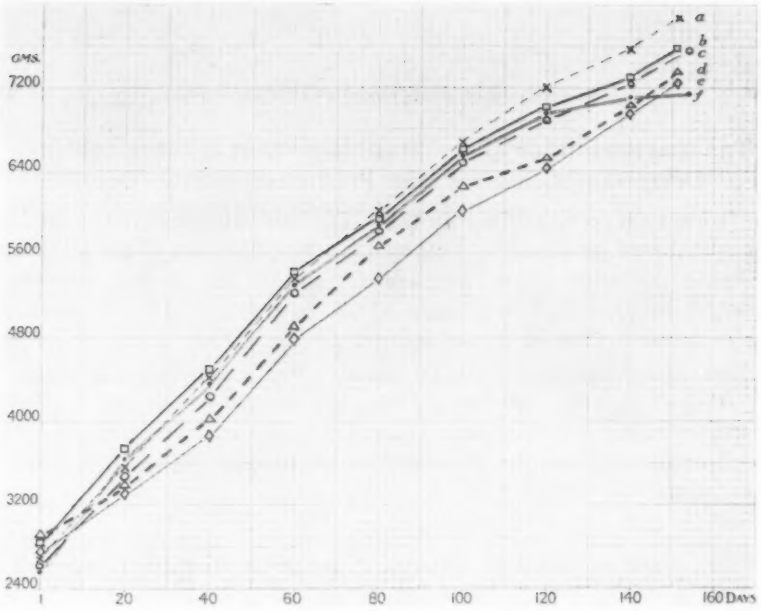

FIG. 6.—Weight curve for Experiment IX. *See also* Fig. 7.

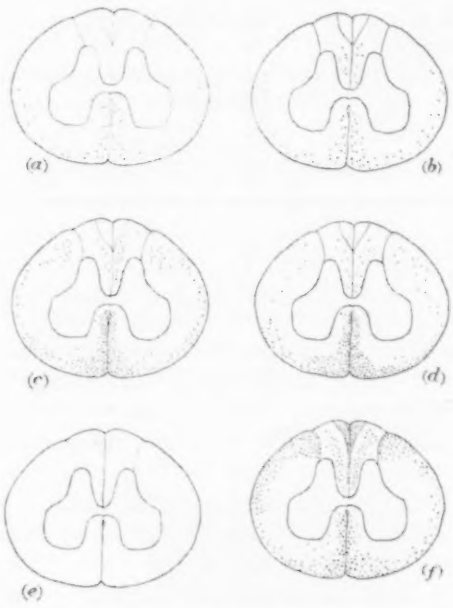

FIG. 7.—Drawings representing the distribution of degenerating fibres as shown by the Marchi technique in the spinal cords at the level of the 5th cervical in (*a*), (*b*), (*c*), (*d*), (*e*) and (*f*) of Experiment IX. (*a*) Petrol ether extract of rye germ; (*b*) control; (*c*) rye germ; (*d*) heated rye germ; (*e*) cabbage (boiled); (*f*) rye germ extracted with petrol ether. Note the greater degeneration produced by rye germ (*c*), heated rye germ (*d*), and extracted rye germ (*f*), while the petrol ether extract of rye germ (*a*) is no worse than the control. The addition of cabbage (*e*) has prevented all degeneration.

The Prevention of Cord Changes by Vitamin A when the Diets are Rich in White Flour and Wheat Germ.

It has been previously shown that: (1) The degenerative changes in the spinal cord produced by diets rich in white flour and wheat germ are prevented by butter but not by olive oil; and (2) the changes produced by ergot are prevented by vitamin A. It now remained to see whether the protective effect of butter against cereals, which it lost on being heated and oxidized (see Exp. 2), was also due to its vitamin A content.

In the following experiment (Exp. 10), the relative defensive effects of irradiated ergosterol (vitamin D), and mammalian liver oil (vitamin A), were compared when the cereal moiety of the diet consisted of 75 per cent. white flour and 25 per cent. wheat germ.

Experiment X.

The Relative Effects of Vitamins A and D on Cord Degeneration produced by Cereals.

Age beginning: 7 weeks.

Duration of experiment: About 4 months.

Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 2-3 grm.

(*a*) had 75 per cent. white flour, 25 per cent. wheat germ.

(*b*) „ 75 „ „ „ 25 „ „ „ and irradiated ergosterol.

(*c*) „ 75 „ „ „ 25 „ „ „ and vitamin A (mammalian liver oil

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Some clinical notes
(*a*)	—	Some degeneration, especially in anterior and antero-lateral columns	Abnormal gait; later hind legs paralysed; had fits
(*b*)	Irradiated ergosterol (vitamin D) 0·05-0·1 c.c.	Rather more degeneration than in (*a*), especially in anterior and antero-lateral columns	Abnormal gait; hind legs stiff and head movements uncontrolled. Could just walk at end of experiment; had fits
(*c*)	Vitamin A oil, 1 c.c. (from mammalian liver)	No degeneration	Fairly active throughout experiment; no inco-ordination

(*b*) and (*c*) increased steadily in weight throughout the experimental period; (*a*) grew well at first but later lost weight.

This experiment shows clearly that vitamin A and not vitamin D prevents the cord degeneration when white flour and wheat germ are the cereals eaten.

Experiment XI shows that the cereal effect can be antagonized by cabbage. Both animals received oatmeal as the cereal of the diet and vitamin D in the form of irradiated ergosterol.

EXPERIMENT XI.

The Prevention by Cabbage of Cord Changes produced by Cereals.

Age beginning: 7 weeks.

Duration of experiment: About 3 months.

Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 3 grm.; irradiated ergosterol (vitamin D), 0·1 c.c.

(*a*) had 80 per cent. oatmeal and 20 per cent. ground wheat germ.

(*b*) ,, ,, ,, ,, ,, ,, 20 ,, ,, ,, ,,

and 50 grm. cabbage boiled half an hour.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Clinical notes
(*a*)	—	Fair amount of degeneration, especially in Cii, anterior, antero-lateral and direct cerebellar regions	Hind legs stiff; later gait incoordinate
(*b*)	Cabbage boiled ½ hour	No degeneration	Gait normal

Both animals grew well until towards the end of the experiment and then lost weight.

It now seemed established that the degenerative changes in the cord could be entirely prevented by vitamin A both when the diet contained ergot and when rich in cereals.

Since the liver is a storehouse of vitamin A, it became a matter of interest to see what happened to these stores when diets respectively rich and poor in this substance were eaten. Did they disappear when the diet was deficient in this respect and did their absence from the liver determine the development of the cord changes? In order to decide this point, the livers of many animals with and without symptoms of cord degeneration were examined for vitamin A. The technique employed was as follows: 20 grm. of liver were heated on a water bath with alcoholic potash; the alkaline mixture was thrice extracted in a separating funnel with ether; the ether was distilled off, care being taken to drive off any moisture, and the colour test of Carr and Price [15], using a chloroform solution of antimony trichloride, was applied to the residue. The intensity of the blue reaction was estimated by means of a Lovibond tintometer (Rosenheim and Schuster pattern), and recorded

in blue units. When this method is used under standard conditions, it is generally believed to give a fairly accurate indication of the amount of vitamin A present in the liver. In the figures recorded in this paper a blue unit is that amount of substance which, dissolved in a 1-cm. cube and treated with antimony trichloride, produces a tint equivalent to one Lovibond unit when viewed through a depth of 1 cm. To convert this figure into the blue units which will probably be officially adopted by the British Pharmacopœia, it should be multiplied by 2·2.

No degenerative changes were found in the cords of these experimental animals except when the liver was denuded of vitamin A. This does not mean that absence of vitamin A from the liver always results in cord degeneration, for, as will be seen later (p. 267), there are cases when, for instance, carotene is a constituent of the diet, where there may be no vitamin A in the liver and yet no degenerative changes in the cord. There are also a few exceptional unexplained cases when there is little or no vitamin A or carotene in the food, no vitamin A in the liver, and yet no cord degeneration. The point that seems clear is that, if there is a store of vitamin A in the liver in these animals, cord changes are not found, and if cord changes are found there is no vitamin A in the liver unless this is given after the changes have developed.

Having shown that vitamin A prevents not only cereals but also ergot from exerting its neurotoxic action, it was necessary to see whether this preventative effect could also be obtained with carotene. Parenthetically it may be stated that when the above-described experiments were made the fact that the vitamin A action of cabbage was due to carotene had not been suggested. The relation of vitamin A to carotene has been under discussion for many years, since Steenbock and Boutwell [16] drew attention to the fact that the colouring matter of foods was often related to their vitamin A content. It was at first thought that carotene might actually be vitamin A. This was soon shown not to be the case, for preparations made from cod-liver oil, although containing abundant vitamin A according to biological tests, were devoid of carotene. The problem was brought to the fore again in 1928, by Euler, Euler and Hellström [17], who found that for growth in young animals carotene could be substituted for vitamin A. This was denied at first by Dulière, Morton and Drummond [18], but confirmed by Moore [19], and by Collison, Hume, Smedley-Maclean and Smith [20]. A further development took place in 1929, when Green and E. Mellanby [21] found that the anti-infective action of vitamin A could be similarly exerted by carotene. Of course, none of these investigations

settled the problem as to whether pure carotene was the active agent and the experience of investigators on the relation of cholesterol, ergosterol and ultra-violet irradiation to vitamin D, has made many hesitate to declare that carotene itself acts like vitamin A and that its effect is not due to some vitamin A impurity. The general trend of results, however, especially those of Euler and his associates [22], suggests that carotene, a chemical substance associated with vegetable life and especially with green vegetables and carrots, has specifically the biological properties of vitamin A. T. Moore [23] has indeed brought forward evidence which suggests that it is the parent substance of vitamin A, and that on giving carotene to animals vitamin A is produced and stored in the liver. In order, therefore, to test the relationship between vitamin A and carotene from quite a different angle, experiments were made to see whether carotene could also prevent the degenerative changes in the spinal cord produced by cereals and ergot.

In the following and other similar experiments, carotene, supplied by the British Drug Houses, was tested to see whether it could prevent the degeneration produced by ergot. Carrots, the richest known source of carotene among vegetable substances, were also tested.

EXPERIMENT XII.

The Prevention of Cord Degeneration by Carotene.

Age beginning: 9 weeks.
Duration of experiment: About 2 months.
Basal diet: White flour, 130 grm.; separated milk powder, 20 grm.; lean meat, 10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; sodium chloride, 3 grm.; irradiated ergosterol (vitamin D), 0·1 c.c.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Vitamin A in liver at F.M. as tested by $SbCl_3$	Some clinical notes
(*a*)	Carotene, 5 mg... Ergot, 2 grm. ..	No degeneration ..	No vitamin A ..	Fairly active. No inco-ordination
(*b*)	Carrots, 25 30 grm. Ergot, 2 grm.	No degeneration ..	No vitamin A ..	Fairly active
(*c*)	Butter, 10 grm... Ergot, 2 grm.	No degeneration ..	Some vitamin A (1 5 Blue Units per grm.	Fairly active. Normal gait
(*d*)	—	No degeneration ..	No vitamin A ..	Fairly active
(*e*)	Ergot, 2 grm. ..	Much degeneration.	No vitamin A ..	Very inco-ordinate. Later lost weight and became weak. Eyes not quite normal

The rate of growth was good in all cases, but (*e*) lost weight later in the experiment. Fig. 8 represents drawings of sections of different levels of the spinal cord

of (*e*), the only animal of this experiment developing cord degeneration. From these drawings the relative distribution in different parts of the spinal cord can be seen.

It is evident that in animals receiving ergot, cord degeneration was prevented by carotene itself and by carrots which contain carotene, and

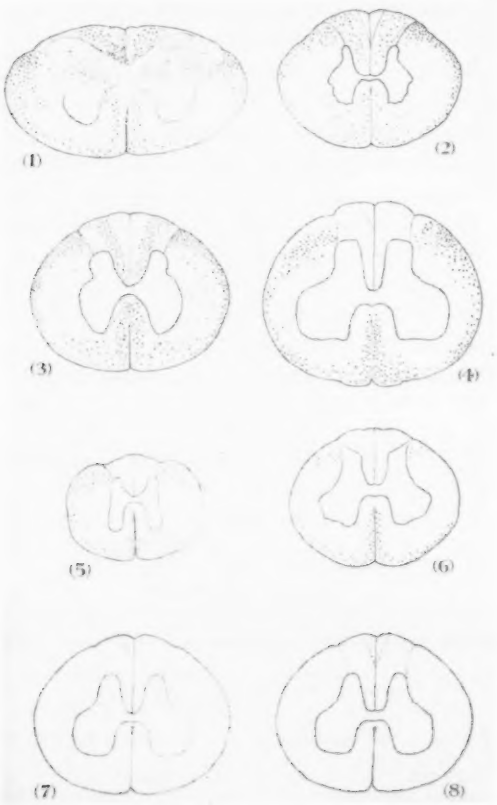

FIG. 8.—Drawings representing the distribution of degenerating fibres as shown by the Marchi technique in the spinal cord at the levels: (1) low medulla; (2) 1st cervical; (3) 3rd cervical; (4) 6th cervical; (5) 12th dorsal; and (6) 3rd lumbar, of animal (*e*) (ergot) of Experiment XII. Sections (7) and (8) show no degeneration in animals (*a*) and (*c*) (cervical region), which received carotene and butter respectively.

by butter, which contains both vitamin A and carotene. No degeneration was found in (*d*), the control animal, which was given neither ergot nor a protective agent. In addition to these facts, there are several other

points of interest about this series of animals. The first is the rapidity with which the cord degeneration can be brought about by ergot under favourable conditions. The feeding period only lasted seven and a half weeks and yet in (*e*), where there was no protective agent in the diet, extensive nerve degeneration developed in all the regions examined, including the medulla.

The second point of interest concerns the vitamin A stores in the liver. These were probably very small at the beginning, otherwise (*e*) would not have reacted so quickly to ergot. It will be further noticed that even when carotene and carrots were ingested there was no vitamin A observable in the liver by the colour reaction of Carr and Price. This fact opens up several questions of interest which, however, can only be touched upon here. It was stated earlier that the store of vitamin A in the liver of the experimental dogs has apparently to be used up before spinal cord degeneration develops. It might be inferred, therefore, that when the vitamin A stores are used up, especially when ergot is in the diet, the nerve degeneration would be evident. This does not seem to happen when carotene is in the diet. It may then be asked why, if carotene is the precursor of vitamin A in the liver, there was no vitamin A in the livers of (*a*) and (*b*), which received carotene and carrots respectively. This question cannot yet be answered. Possibly, if larger doses of carotene or carotene-containing substances had been given to these animals, a store of vitamin A would have been produced in the liver. Apparently carotene can act immediately after absorption from the alimentary canal either, as seems probable, directly, or after conversion to vitamin A, and thereby protects the nervous system from the toxic action of ergot. An analogous phenomenon is seen when carotene acts either prophylactically or curatively in bacterial infection in animals (Green and Mellanby [21]). Animals may be fed on diets deficient in vitamin A and so lose their stores. If carotene in sufficient quantity is now given, no infective lesions will develop, or if they have developed, will disappear, and yet the livers will often be found post-mortem to contain no vitamin A. Here, as in the degeneration experiments, although no vitamin A can be found in the liver, carotene exerts its anti-infective action and prevents epithelial hyperplasia.

Moore's results [23], in which he got evidence of the change of carotene to vitamin A in rats, have already been referred to above. The curious thing about experiments of this nature, as my colleague Green and I [21] have previously pointed out, is that surprisingly large quantities of carotene have to be given to these animals before vitamin A can be

found in the liver—much more, in fact, than is necessary to clear up all signs of vitamin A deficiency.

The Antagonism between the Nerve Toxin and Vitamin A and Carotene.

The foregoing results and others of a similar nature show that demyelination of the cord fibres is controlled by at least two factors—a positive harmful influence and the absence of a defending chemical mechanism—and this clarifies the problem to some extent, although of course it leaves much obscure.

The double mechanism may well explain, for instance, the difficulties earlier workers had in producing demonstrable cord changes in nervous ergotism, for at that time not only were vitamins unknown but the protective action of specific food elements was unheard of.

A second difficulty, which is also at least partially explained, is that referred to above (p. 251) in connection with the original experiments in which inconsistent results were obtained in different litters when cereals alone were employed. It appears that the variation in the results must have depended to some extent on the initial stores of vitamin A in the puppies of the different litters at the beginning of the feeding period. The liver is the main organ in which vitamin A is stored and the amount stored in this organ in different animals varies greatly. Sometimes it may be as high as 1,900 blue units per gramme of liver and sometimes it is almost negligible in amount or even absent. The amount in the liver depends on the amount of vitamin A and carotene included in the animal's food. If, for instance, puppies have been fed during the pre-experimental periods on diets containing cod-liver oil, butter and egg-yolk, their livers are very rich in the substance. The relation of the storage of vitamin A and the development of nervous lesions was investigated and it was found that when the pre-experimental diet was rich in vitamin A the time required for the production of nervous symptoms was lengthened. Thus the development of symptoms depends not only on the deficiency of vitamin A and carotene from the diet but also on the time it takes for the stores of the vitamin in the body to be used up. As might be expected the time of denudation varies greatly according to the original stores. In some cases this period may be several months and in others a few weeks. It is advisable, therefore, in experiments of this type to control the pre-experimental diet in order to ensure as far as possible similar reactions to the experimental feeding in point of time and intensity. There is also some evidence which

suggests that good feeding in the sense described, if continued long enough, may confer immunity against the neurotoxins for a long time after the liver vitamin A stores are completely denuded.

The protective action of carotene on the nervous system supports the suggestion that this substance and vitamin A are physiologically similar although not identical chemically. The action of carotene must also be taken into account in considering the effect of cereals of which it is sometimes a constituent. For instance, apart from the influence of the varying stores of vitamin A in the livers of different litters of pups, referred to above, it seemed possible that the irregularity of results in the cereal experiments might be influenced by (1) the presence of traces of carotene in the samples of wheat germ, or by (2) varying amounts of toxic factor in the different samples, or both. Examination of wheat germ for carotene revealed that there is a certain amount of this substance present and it is probable that it prevents in some degree at least the spinal degeneration. My colleague H. N. Green has estimated that 100 grm. of wheat germ contained about 1 mg. of carotene. Whether this amount varies in different specimens, and whether the variation is of significance in explaining the results obtained, is not known. One milligram increase in carotene intake daily would certainly modify the experimental results. It is of interest to note that rye germ was found by Green to contain only half the carotene found in wheat germ.

Although the cereals have not been systematically investigated in this respect, experiments were made in which yellow and white maize formed the cereal element of the diet. Yellow maize has for many years been given in diets as a source of vitamin A (Steenbock and Boutwell [16]), but this quality is almost certainly due to its carotene content, which is large for a cereal. White maize, on the other hand, contains little or no carotene. It would be expected, therefore, that it would be more difficult to produce cord degeneration in dogs when the cereal of the diet consisted of yellow rather than white maize. This is certainly the case, and in preliminary experiments it has not only been impossible to produce the degenerative changes with yellow maize, but even where ergot was added to the diet there was sufficient carotene in the yellow maize to prevent the ergot neurotoxic action (see Exp. XIII below). The difference in the condition of animals when yellow or white maize is added respectively to diets otherwise deficient in vitamin A and carotene is great and, so far as is known, this difference is due entirely to the carotene in the yellow maize. This point will be

referred to again in the discussion on the possible bearing of these results on pellagra.

The following experiment illustrates the protective effect of yellow maize against ergot and, in addition, shows that when white maize forms the cereal basis of a diet deficient in vitamin A and carotene, spinal cord degeneration develops:—

EXPERIMENT XIII.

The Relative Effects of White and Yellow Maize.

Age beginning: 10 weeks.

Duration of experiment: About 3 months.

Basal diet: Separated milk powder, 20 grm.; lean meat, 20-10 grm.; peanut oil, 10 c.c.; dried yeast, 2·5 grm.; orange juice, 3 c.c.; salt, 3 grm.

Animal	Diet variable	Cord degeneration as shown by Marchi staining	Some clinical notes
(*a*)	White maize. Irradiated ergosterol.	Some degeneration	Quiet and dazed; stupid appearance. Gait not normal. Ulcer on eye
(*b*)	White maize. Irradiated ergosterol. Ergot, 2 grm.	Much degeneration; little anterior and antero-lateral; big patch in Burdach	Legs spastic; inco-ordinate. Head positions abnormal; looks stupid
(*c*)	Yellow maize, Irradiated ergosterol. Ergot, 2 grm.	No degeneration	Normal

"CURATIVE" EXPERIMENTS WITH SUBSTANCES CONTAINING VITAMIN A AND CAROTENE.

It has been shown that substances containing vitamin A, such as butter, egg yolk, mammalian liver oil and also carotene and carotene-containing foods including cabbage and carrots, prevent ergot and other toxins from attacking the nervous system and from producing nerve degeneration in the spinal cord. The problem then arises as to what happens if the animals are given ergot with a diet deficient in vitamin A and carotene until signs of nerve degeneration develop and are then given these substances in abundance? In other words, are vitamin A and carotene curative as well as protective in their action? There is definite evidence that the clinical condition tends to clear up rapidly under these conditions, though the degree of improvement naturally depends on the extent of the initial lesion. The immediate effect is often astonishing even when the animal has been paralysed for a long time. In a week or two animals with weak or even paralysed hind legs

become active once more. At first the activity brings out more prominently the inco-ordination and the animals run about with an intoxicated gait. Usually this diminishes greatly and in some cases the animals may later appear almost normal. Presumably further degeneration ceases on giving the additional vitamin A or carotene, and the fibres already showing degeneration are gradually absorbed.

One animal which, although it had been unable to stand for some months, and showed great spasticity especially when held in the standing position, was given vitamin A prepared from mammalian liver. After three weeks the animal could stand but was very inco-ordinate when it attempted to walk. Two months of vitamin A feeding resulted in a very active animal but there was still some inco-ordination which, however, further diminished by the end of the experiment three months later, but, as might be expected, gait never became normal. Examination of the spinal cord by Marchi's method showed complete absence of fibres with demyelination. Areas of sclerosis were found by Weigert's method of staining, indicating that the degenerating fibres had disappeared and had been replaced by neuroglia. Presumably other tracts took on the function of the injured ones and the animal relearnt to walk more or less normally.

The cord of another animal which had received 5 mg. of carotene daily for seventeen days after the development of severe ergot symptoms was kindly examined histologically by Dr. Perdrau. In this period the animal made great clinical improvement but the cord still showed a large number of degenerating fibres when stained by Marchi's method, and areas of more complete degeneration when prepared by Weigert's method.

The first rapid improvement which follows the giving of vitamin A or carotene, especially as regards activity, may depend upon some action of these substances on the muscle itself, but the gradual and continuous improvement which develops later is undoubtedly due to a better functioning of the central nervous system itself. It is clear that vitamin A and carotene not only prevent the cord changes produced by ergot but that they exert a "curative" effect after development of these changes in the sense that great clinical improvement with increased activity and diminished inco-ordination takes place after their administration. In course of time all active degeneration of the nerve fibres in the cord disappears and demyelination demonstrable by Marchi's technique can no longer be found.

There are few more striking effects in animal nutrition than the

improvement brought about by the daily addition of 5 mg. of carotene to an animal suffering from severe nervous ergotism.

Clinical Condition and Degeneration Changes in the Cord.

The main clinical symptoms in the affected dogs are spasticity, especially of the hind limbs, and inco-ordination in walking and running, which may, however, especially if the experiment is prolonged, be masked by weakness. Often the head is held on one side and the ears are awry, giving the animal a weird appearance. In the early stages

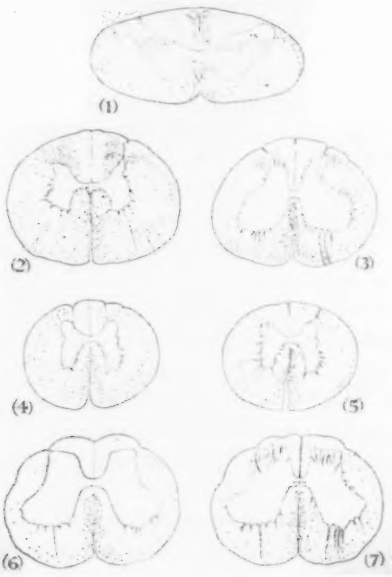

Fig. 9.—Drawings representing the distribution of degenerating fibres as shown by the Marchi technique at different levels of the spinal cord of an animal which had received ergot and no vitamin A or carotene. The levels represented are: (1) medulla; (2) 2nd cervical; (3) 6th cervical; (4) 2nd dorsal; (5) 11th dorsal; (6) 3rd lumbar; (7) 4th lumbar. Note the differences in distribution of degenerating nerve fibres at the different levels, especially the variations found in the posterior columns.

the animal usually has a pica and runs about apparently looking for suitable food and in so doing attempts to eat anything it comes across. At a later stage it seems incapable of fixing its attention for more than a moment and lurches about with no apparent object, and looks stupid. At a still later stage weakness, especially of the hind legs, becomes more apparent and the animal remains standing, often with legs apart and

spastic. After passing through a stage when it prefers to sit and make no effort to move, it may become paralysed. The eyes often develop pathological changes and the inco-ordination then appears more prominent owing to defective vision. At any time convulsions may occur.

The difficulty of describing in summary the positions of degeneration arises more particularly from the fact that often the amount of degeneration in the same tracts varies to some extent from level to level and degeneration may be evident in a tract at two levels in the

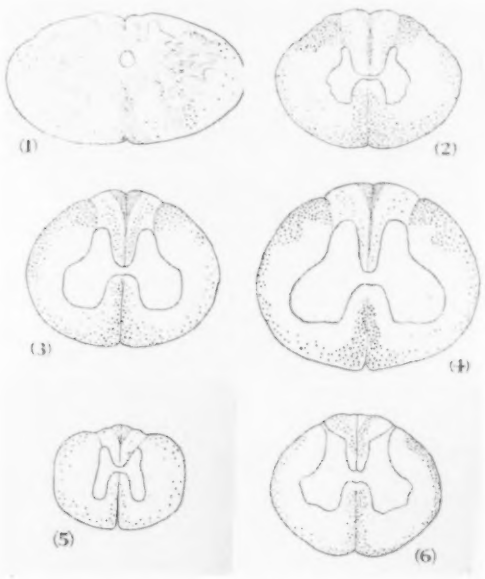

FIG. 10.—Drawings showing degenerating fibres at different levels of the spinal cord as prepared by the Marchi technique. The levels represented are: (1) medulla; (2) 2nd cervical; (3) 4th cervical; (4) 6th cervical; (5) 7th dorsal; (6) 4th lumbar. The column of Goll in this animal shows degeneration—a relatively rare occurrence.

cord whereas at an intermediate level little or no degeneration may be found in the corresponding area.

Thus, of all cords examined up to the present time and showing degeneration in the region of the first cervical, 72 per cent. of cases had degenerated fibres in the column of Burdach, whereas in the same cords in the region of the sixth cervical only 52 per cent. showed degeneration in this tract. Again in the direct cerebellar tract: 44 per

cent. of sections of the first cervical region showed degeneration; 62 per cent. of sections of the third cervical region showed degeneration; 36 per cent. of sections of the sixth cervical region showed degeneration. This irregularity in the appearance of degeneration is apparently a

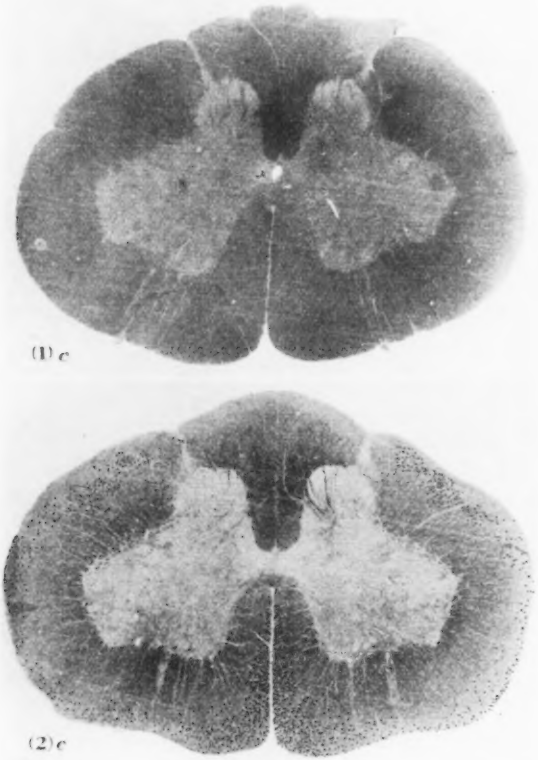

FIG. 11.—Photomicrographs of sections stained by Marchi technique of animals (*c*) and (*e*) of Experiment XII at a level of the 6th cervical. Note the absence of all degeneration from (1) (carotene plus ergot) and the abundant degeneration in (2) (ergot). (Retouched.)

condition also found in the demyelinated fibres of sub-acute combined degeneration associated with pernicious anæmia.

Some other points as regards areas of degeneration demonstrated in these experiments by the use of Marchi and Weigert stains may be mentioned:—

(1) Degenerative changes are more prominent in the cervical than in the lumbar region (fig. 9).

(2) The anterior columns are most affected whichever region of the cord is investigated (fig. 10).

(3) The anterior columns (represented in the human cord by the direct pyramidal tract, a tract said not to be present in the cord of the dog), the antero-lateral tract, especially superficially, the column of

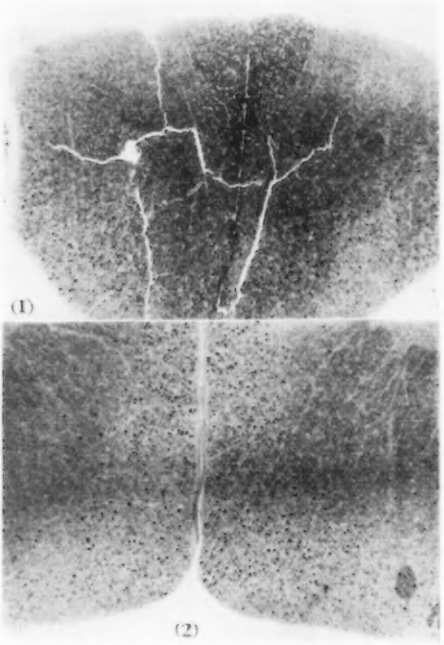

FIG. 12.—Photomicrographs showing cord degeneration by the Marchi technique in (1) posterior columns (note the degeneration in Goll's column) and (2) anterior columns.

Burdach, and the direct cerebellar tracts are the positions most commonly associated with degeneration. In the direct cerebellar tract, the degenerated fibres are often found near the surface, but sometimes they are deeper, away from the surface, whereas sometimes both areas are affected. The fibres of Goll's column are not often affected.

(4) The crossed pyramidal tracts are usually but not always free from degeneration.

(5) The indications are that the ascending fibres of the cord are more particularly picked out, including those passing to the cerebellum.

Areas of degeneration at different levels in the cord can be seen in figs. 9 and 10. The point of interest of fig. 9 is that it shows degeneration in the column of Goll, a rare occurrence in these experiments.

The spasticity of the limbs suggested that the upper motor neurone would show extensive degeneration, but this does not appear to be the case. It seems possible that the spasticity may ultimately be related to

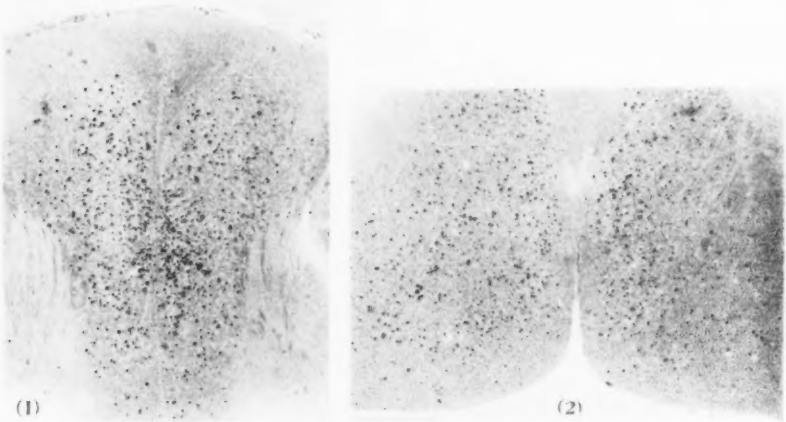

FIG. 13.—Photomicrographs of the spinal cord at the level of the 1st cervical, stained by Marchi technique. (1) Posterior columns (degeneration in Burdach only, the usual occurrence) and (2) anterior columns.

changes in the cord and mid-brain concerned with posture but nothing definite can be said yet on this point. Neither the upper parts of the brain nor the mid-brain has yet been fully examined histologically. The fits, stupid appearance, inco-ordination and loss of balance suggest that further extension of the examination to the upper parts of the central nervous system will show degenerative changes.

The changes in the cord do not seem to be accompanied by any cell invasion or other indication of an inflammatory nature. Neuroglial overgrowth in the positions of degeneration is not great but the blood-supply to these areas appears in Weigert-stained sections to be increased. Probably the relative smallness of sclerotic growth is due to the shortness of the experiments. In longer experiments, e.g., thirty-

one weeks, larger areas of degeneration can be seen when the cord is stained by Weigert's method.

The distribution of cord degeneration suggests strongly that the fibres going to the cerebellum are involved. The clinical condition (inco-ordination, loss of balance) also agrees with this suggestion.

The relation of the clinical condition to the cord changes is not easy to interpret, partly because of the interference of other factors and

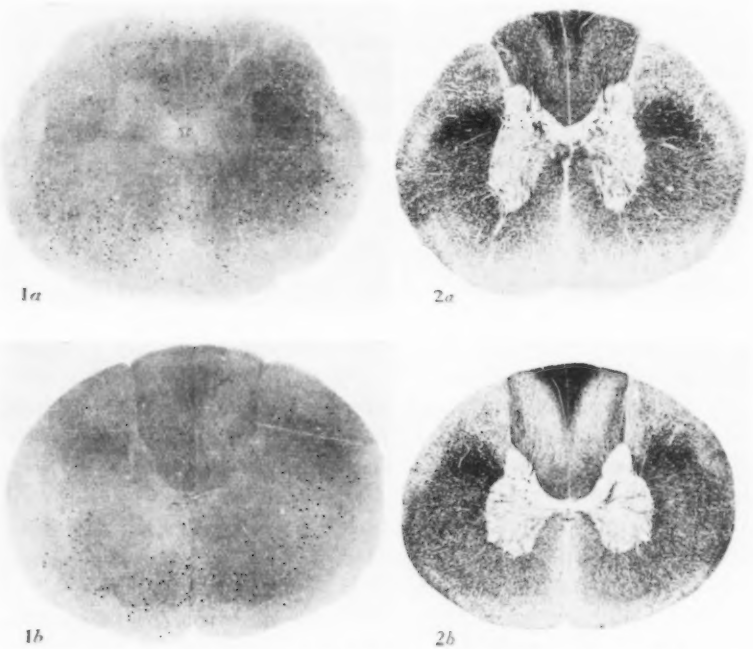

FIG. 14.—Photomicrographs of the 2nd and 4th cervical regions of one cord showing degeneration by (1) Marchi and (2) Weigert technique, respectively, after about five months of ergot feeding (without vitamin A or carotene). 1 (*a*) and 2 (*a*) are photographs of the 2nd cervical level; 1 (*b*) and 2 (*b*) of the 4th cervical level.

partly because of the obvious difficulty of investigating sensory changes in animals. For instance, muscular weakness is undoubtedly to be partly explained by the intrinsic failure of the muscle and may be independent of nervous defect. Again, pathological changes in the eyes are often found which interfere with vision. Sometimes the eyes are affected by xerophthalmia due to a deficiency of vitamin A, but in dogs

receiving a diet deficient in this vitamin and containing ergot another inflammatory condition of the eyes, often affecting the conjunctiva and becoming in some cases suppurative, is sometimes seen. Together with the conjunctivitis, a vascularized keratitis may develop. (I am indebted to my colleague, Mr. Wellwood Ferguson, for examining the eyes of some of these animals.) In one group with vascularized keratitis examined by him, no organisms were grown from the pus exuding from the eyes). This suppurative condition of the conjunctiva and cornea is rarely seen in experimental dogs except when ergot is given, and no doubt this substance plays a specific part in its development. In view of the well-known relation of vitamin A to hemeralopia, it is also probable that the vision is affected more centrally in many of these animals. An attempt to disentangle the relation of all these pathological changes to the behaviour of the animals is now being made.

The Possible Bearing of the Results to Nervous Disease in Man.

The question now arises as to what bearing these experimental results have on human nervous diseases.

Convulsive ergotism.—The above described results are probably of immediate application to the condition of convulsive ergotism in man which appears occasionally in epidemic form in rye-eating countries. They suggest an explanation as to why such epidemics only appear in times of famine and poverty. The explanation usually given is that people eat more ergotized bread during such periods, but this, though true in itself, probably only plays a comparatively small part in the problem. If the people eating ergotized rye bread also received sufficient of the protective foods such as green vegetables, butter and egg-yolk containing vitamin A and carotene, no nervous symptoms would, on the basis of the experiments, be expected to develop. Since spinal cord degeneration has been found to develop in many animals in the absence of vitamin A even when no ergot was included in the diet, it is probable that in human beings also the pathological changes ascribed to ergot may in some cases be due to unergotized rye bread itself when eaten under conditions of restricted protective foods. Another point of interest is that in epidemics of nervous ergotism some members of a family may be attacked and others escape. The reason for this indiscriminate picking out of individuals may be related to the reserves of vitamin A in the livers of the individuals. In my experience with dogs, I have found degenerative changes in the spinal cord only when

the liver was depleted of vitamin A. The periods required for this depletion vary greatly in animals according to the other factors of the diet and to the amount of vitamin A initially stored, and the latter will be a crucial factor in the time of onset of nervous ergotism in individuals.

If the experimental results can be directly extended to human nervous ergotism, as seems likely, they indicate that not only can the condition be prevented by supplying foods containing vitamin A and carotene, but also that when the condition has developed immediate improvement in health will follow the administration of such foods. Complete cure is unlikely since nerves in the central nervous system cannot regenerate, and the extent to which function returns will depend on the extent and intensity of the nerve degeneration at the beginning of treatment, but in animals at least the "curative" effect as indicated by clinical improvement is very great.

Pellagra.—The cord changes produced in some of the experimental animals are so similar to those associated with pellagra in man, and the mode of producing them is so closely related to the conditions conducive to this disease that it is difficult to avoid the assumption that they throw new light on its ætiology. Like convulsive ergotism, pellagra is a disease of poverty and is often but not exclusively found among maize-eating populations, and especially in the southern part of the United States. Two types of pathological change are found in this disease—one affecting the skin, especially the hands and parts of the body exposed to sunlight, and the second affecting the nervous system and producing both cerebral and cord symptoms. It is natural to suppose that the skin changes are secondary to those of the nervous system, and indicate a release of the trophic control of the affected skin areas. On the other hand, the two types of change are sufficiently dissociated in many cases as to suggest that two mechanisms are responsible—the breakdown of one resulting in the skin changes and of the other the nervous changes. Experimental evidence also supports the suggestion of a double mechanism which may, however, in some way at present unknown work in harmony. Since the work of Goldberger and Tanner [24] it has been widely accepted that pellagra is a deficiency disease due to the absence from the diet of sufficient vitamin B_2 (or vitamin G of the U.S.A.). This conclusion depended on the curative effects on the skin lesions of pellagrins produced by a series of substances such as yeast, meat and milk. The group of foods having this curative effect was such as to preclude the action being due to a then known vitamin, and the

hypothetical active substance was called the P-P, or pellagra-preventing, factor. Confirmation of this work from another angle seemed to be forthcoming in animal experimental work. The condition known as "black tongue" in dogs was regarded by Goldberger, Wheeler, Lillie and Rogers [25] as analogous to pellagra in man and reacted to the pellagra-preventing factor as did pellagra itself. Goldberger and Lillie [26], and also Chick and Roscoe [27], extended the investigations to rats and in consequence of the skin lesions produced in rats by diets deficient in vitamin B_2, Chick and Roscoe called this substance the anti-dermatitis factor. Recent work described by Aykroyd [28] has, however, led to some doubt as to the identity of vitamin B_2, in so far as the properties of this substance have been elucidated by rat-feeding experiments, and the P-P factor and the problem must still be regarded as unsettled.

Now the results described above suggest that vitamin A or carotene also plays a part in the prevention of pellagra or at least in its nervous manifestations. There is no reason to believe that the experimental diets of the dogs were deficient in vitamin B_2 for they contained separated milk, yeast, meat and often wheat germ, all sources of this substance. On the other hand, sources of vitamin A or carotene prevented the nervous degenerations completely, so that it seems probable that pellagra is due to a double deficiency in the food—the skin changes resulting from a B_2 deficiency and the nervous changes from an A deficiency. The experimental results described above in which the effect of yellow and white maize were compared, confirm the suggestion that a deficiency of vitamin A and carotene is the cause of the nervous changes in pellagra. Yellow maize containing carotene did not allow the spinal changes to occur, but actually prevented such changes being produced even by ergot. When white maize formed the cereal basis of the diet the nerve degeneration appeared (see p. 272). Again, the geographic distribution of pellagra in man seems to be in accord with these results. In America, and especially in the Southern States of the U.S.A. where pellagra is very prevalent, white maize or corn is generally eaten. In Java and the Dutch East Indies where yellow maize is eaten (although how extensively as compared with white maize I do not know), Jansen and Donath [30] report that pellagra is almost never seen. The above suggestions also receive support from observations published in 1928 by Underhill and Mendel [31] who described the effect of various substances, and especially of carotene (5 mg. daily), in curing black-tongue in dogs, a condition referred to above as being cured by the P-P factor of

Goldberger. Underhill and Mendel [31] confined their attention particularly to the mouth and alimentary canal and general condition of the experimental animals, and did not examine the nervous system. Incidentally, it is clear that the condition of "black tongue" as investigated by these various workers cannot be the same disease.

The final point as regards the ætiology of pellagra requiring consideration is whether maize or other cereals play an active part in the development of the disease owing to the presence in it of a toxic factor. Some of the experimental results above described suggest such to be the case. If this is true, then the embryo of the maize is probably richer in this toxic substance than the endosperm. I attempted to test this point experimentally but the results were too indefinite to allow any conclusions to be drawn.

To sum up, the evidence suggests strongly that a deficiency of vitamin A or carotene is the deciding factor in the development of nervous degenerative changes in pellagra. Deficiency of the pellagra-preventing factor seems to be responsible for the skin changes and there is a possibility that a toxic element in maize and other cereals, which is ineffective in the presence of sufficient vitamins A and B_2, must receive consideration. It seems probable that pellagra can be completely prevented and cured by the inclusion in the diet of green vegetables, carrots, milk, butter, egg yolk and mammalian liver. It is possible that, when the condition is very severe, the alimentary disorder may prevent the absorption of these foodstuffs and, if so, it will be necessary to inject carotene or concentrated vitamin A preparations intravenously.

Lathyrism.—Lathyrism, so extensively seen in India, is a disease of which I have no direct knowledge, but the clinical and pathological descriptions and history suggest that the experimental work on dogs may also throw some light on its ætiology and treatment. Clinical descriptions of lathyrism and the dietetic conditions under which it develops have been published by Stockman [32] and Acton [33] and others. The main facts appear to be that it develops in people: (1) who eat largely of lathyrus sativus peas; and (2) in times of famine and drought when their diet is largely restricted to these peas.

There is still some doubt as to the causal agent of lathyrism. For instance, Anderson, Howard and Simonsen [34] found that the seeds of khesari (*Lathyrus sativus* L.) were harmless to ducks and monkeys, whereas akta (*Vicia sativa* L. var. *angustifolia*) produced symptoms in pigeons, ducks and monkeys. Attempts have been made by Stockman

[35], Dilling [36] and Acton and Chopra [37] among others to isolate a toxic agent from lathyrus peas. Stockman [35] found an alkaloid in small quantities which he thought might be responsible for the condition; Acton and Chopra [37] found an amine, and Anderson, Howard and Simonsen [34] thought that the base divicine found in akta might be the toxic agent. Dilling [36] isolated two alkaloids in very small quantities which caused increased spinal reflexes followed by paralysis in frogs, and weakness and paresis of the hind limbs of mice. Acton and Chopra [37] state that the toxic factor can be removed from the peas by soaking them in water.

Experimental work on animals with the object of producing lathyrism has never been very satisfactory. In no case, so far as I know, has good evidence been adduced that the weakness and spasticity produced in animals by diets containing lathyrus peas or by injecting chemical preparations made from these peas are associated with the degenerative cord changes seen in human lathyrism. Many of the experimental diets used by workers have been so defective that it would be surprising if the animals had not developed severe illness independently of the specific signs and symptoms of lathyrism. With the knowledge now at hand it ought to be simple to produce in experimental animals the spinal cord degeneration found in human lathyrism if the diets are more complete than those previously used by investigators and yet deficient in vitamin A and carotene. I have not yet been able to investigate this problem owing to the difficulty of getting a supply of the peas, but in a casual experiment I was interested to find characteristic cord changes in one animal whose diet consisted of beans 30 to 150 grm., separated milk powder 20 grm., meat 10 grm., yeast 5 grm., orange juice 3 c.c., sodium chloride 1 grm. (see Exp. XIV). Whether this result was due only to a deficiency of vitamin A, or to this deficiency acting in association with a toxic factor in the beans, cannot be stated. Another dog on a similar diet with the addition of cod-liver oil did not develop any degenerative changes in the spinal cord. The beans used in this experiment were dried haricot beans. Animals receiving dried peas did not, during the short period of the experiment, show any degenerative changes. I hope, however, to be able to investigate this problem in the near future.

It ought also to be an easy matter to see whether vitamin A or carotene has the specific curative and preventive effect in human lathyrism. As the result of a field study of lathyrism in India, Young advanced the suggestion that lathyrism is primarily a deficiency

disease, and that vitamin A deficiency is the factor concerned. While the facts adduced by Young could be equally well used to support the possibility of other deficiencies being responsible for this disease—for instance, a deficiency of vitamin B_2—the experimental results above described are in support of Young's suggestion.

Experiment XIV.

Spinal Cord Degeneration in a Dog whose Diet included Dried Haricot Beans.

Age beginning: $10\frac{1}{2}$ weeks.
Duration of experiment: About 3 months.
Basal diet: Separated milk powder, 20 grm.: lean meat, 20-10 grm.: peanut oil, 10 c.c.: orange juice, 3 c.c.: dried yeast, 2·5 grm.: salt, 2 grm.: irradiated ergosterol (vitamin D) 0·05-0·1 c.c.

Animal	Diet variable	Cord degeneration as shown by Marchi staining in sections examined	Clinical notes
(*a*)	Dried beans	Degeneration in anterior, antero-lateral columns and direct cerebellar	Very quiet: gait not normal, but no very definite symptoms noticed
(*b*)	Dried beans Cod-liver oil	No degeneration	Normal

Cord Changes in Pernicious Anæmia.

Finally, the problem arises as to whether these experimental results have any relationship to the subacute combined degeneration of the cord associated with pernicious anæmia. It must be stated at once that the discussion on this point is largely hypothetical, and my own observations on this disease, although of an elementary nature, make it clear that the problem in this case is not so directly related to the animal results as are convulsive ergotism, lathyrism and pellagra. At the same time the demyelination of the cord fibres often found in pernicious anæmia is so characteristic a change that its production and prevention by the above described methods suggest that there may be a similar specific factor or factors involved in both the clinical and the experimental conditions. Nor is the exceptional nature of this pathological condition the only reason for suspecting some common factors in ætiology. Whatever the primary cause of pernicious anæmia may be, there seems little doubt that the liver is implicated in this disease since the administration of liver (Minot and Murphy [39]), by supplying a hormone (a compound containing β-hydroxyglutamic acid (West and Howe [40]) and ι-γ-hydroxyproline (Dakin, West and Howe [41]), brings about great improvement in the blood condition. There is,

however, general agreement that watery extracts of liver, while they cure the blood condition over the period, do not stop the degeneration of the cord. Indeed, it is said that the nervous symptoms are often more severe to-day, since the liver treatment was introduced, than they were previously; for, whereas the blood condition is generally brought back to normal by liver extracts, and the life of the patient lengthened, the cord changes become progressively worse. Ungley and Suzman [42] have recently found that whereas the nervous symptoms often become worse during treatment with liver extracts, curative changes and general improvement both in the blood-picture and in the nervous condition result when whole liver is administered. If this is the case, it seems probable that the substance present in the whole liver, and absent from the extracts of the liver, acting in this way on the nervous system, is vitamin A. My own experience in connection with the cord changes of pernicious anæmia is very small. The nervous symptoms in one patient under my charge suffering from pernicious anæmia became definitely worse when ordered whole liver, and later, liver extract and cod-liver oil. Unfortunately, she was an out-patient during treatment, so that it is very difficult to make any deductions from this case. She was admitted to hospital later in a comatose condition, with a bacterial infection of the kidneys, and post mortem her liver contained only a small amount of vitamin A (79 blue units per gramme), although much more would have been expected in view of her suggested treatment.

It appeared to me at one time possible that the liver in pernicious anæmia could not store vitamin A in a normal way, but this cannot be always the case because in another patient suffering from pernicious anæmia who had died of a pyelo-nephritis the liver was found to be very rich in vitamin A (10,560 blue units per gramme of liver). This liver was kindly sent to me by Dr. Perdrau. It is possible, of course, that although the pernicious anæmia patient may be able to store vitamin A, there is sometimes a failure of an unknown nature which prevents this substance exerting its normal function on the central nervous system. An analogous instance suggesting the possibility of such an explanation is seen in diabetes mellitus, since, according to Pollak [43], the pancreas of patients deceased of this condition usually contains insulin in fair quantities, i.e., roughly half that of normal people.

The two main pathological conditions associated with pernicious anæmia, i.e., the blood changes and the cord changes, so often develop independently and react so differently to treatment that the idea that each is controlled by a separate chemical mechanism seems likely. It

would certainly be interesting if both of these chemical failures could be associated with failure of one organ, viz., the liver. It is obvious, however, that the known facts of this problem are too few at present to allow anything more than surmise, but the hypothesis has sufficient support to warrant further investigation along these lines.

It is also clear that there is a possibility of a relationship between this experimental work and other clinical conditions associated with degenerative changes in the spinal cord. Subacute systemic lesions of the cord, regarded by Orr and Rows [5] as falling in the hæmatogenous category, are also found in Addison's disease and cancer cachexia, and it would be of interest if it were found that carotene and vitamin A prevented or influenced these changes. On the other hand, there are the degenerative cord changes found in tabes dorsalis and general paralysis and said by these same workers to arise from toxins ascending the peripheral nerves in the lymph stream, which must receive consideration from this new angle. Again, the well-known remissions seen in disseminated sclerosis suggest that there may be some protective mechanism of the nervous system such as is exerted by carotene and vitamin A, which at times comes into action and not only prevents extension but even, in the early stages at least, has a curative influence. It is evident that in this clinical condition also the protective effect of these substances is worth testing. It may be, of course, that the protective influence of carotene and vitamin A can only be exerted in the case of specific nerve toxins obtaining access to the nervous system in a particular way, for instance, via the blood-stream and not via the lymph. Or, it may be that they readily antagonize and prevent the changes associated with a high cereal diet and ergot but give no protection against the toxin of treponema pallidum or that producing disseminated sclerosis. At all events these points can be easily tested clinically.

It is true that so far as this experimental work is concerned pathological changes in the spinal cord have only arisen as the result of a gross deficiency of vitamin A or carotene in the diet. It is doubtful, however, whether under ordinary dietetic conditions a deficiency so intense is of common occurrence in this country. On the other hand, an insufficiency of vitamin A and carotene in the general diet of highly organized communities is undoubtedly very widespread. The question arises as to whether the partial deficiency of these protective substances is responsible for slighter, but possibly more frequently seen, abnormalities of the nervous system. For instance, the effect of deficiency in

vitamin A intake in producing epithelial hyperplasia often associated with bacterial invasion suggests that this substance may have a similar influence on the development of nervous tissue. Women in pregnancy not only have to be provided with sufficient vitamin A to keep their own tissues working but must themselves pass on large quantities to the developing fœtus. Does the nervous system of the infant suffer when this supply is deficient? How such a partial deficiency of vitamin A or carotene might influence the human nervous system at different periods of life is not known. Anybody with experience of feeding young animals on experimental diets must be impressed by the difference in energy and activity among puppies brought up respectively on diets rich and poor in vitamin A. Similar differences in human dietary in early life may be of equal significance.

As regards the effect of gross deficiency of vitamin A described above, although all attention has been given to the spinal cord it must be added that the mental changes evidence by the general behaviour of the animals are also great and demand investigation. It is indeed clear that the functioning of the more highly developed parts of the brain is greatly influenced by dietetic constituents and the possibility that cerebral development and activity are to some extent retarded by dietetic defects short of those tested in this experimental work must be borne in mind.

One final point must be referred to. The anti-infective action of vitamin A and carotene is on a firm experimental basis. Clinically the uses and limitations of this action have not been worked out, but even so experience indicates that the phenomenon will undoubtedly prove to be of significance in the case of some human infections. The question presents itself, whether the protective effect of vitamin A and carotene against demyelination of nerve fibres and their anti-infective action against some kinds of bacterial infection may not have special significance in the case of the nervous system. Is it not possible, for instance, that the beneficial effect of the malarial treatment of general paralysis of the insane is due to the liberation of large quantities of vitamin A and other protective factors from the livers of patients infected with the malarial parasite? It might be worth while before giving malarial treatment in such patients to fill their liver up with this vitamin by giving diets rich in this substance and cod-liver oil. It is possible that the uncertainty of this strange form of treatment would disappear if this factor were taken into consideration.

The foregoing experimental work demonstrates that nutritional influences on the central nervous system, both in the sense of protec-

tive and harmful action, are sufficiently important to warrant their consideration in the clinical investigation of many pathological changes of the nervous system.

Summary.

(1) When diets containing a large amount of cereal (other than yellow maize) and deficient in vitamin A or carotene are eaten by young puppies, degenerative changes in the spinal cord in the form of demyelination of the nerve fibres, which can be readily observed by Marchi's method of staining, can generally be observed.

(2) The addition to the diet of 2 to 5 grm. of ergot daily under these conditions hastens and intensifies these degenerative changes. Rye germ also hastens the changes and in some experiments wheat germ has been found to have a similar but less pronounced effect.

(3) The presence in the diet of any rich source of vitamin A such as liver oil (mammalian or fish), whole milk, butter or egg yolk or some source of carotene such as green vegetables or carrots, or carotene itself, prevents or diminishes these degenerative changes even when ergot is eaten.

(4) Spinal cord degeneration of this type does not seem to develop until the reserves of vitamin A in the liver are dispersed. Since these stores may be very large in well-fed animals, the time of onset of the symptoms of spasticity, inco-ordination and weakness varies greatly in different litters of animals. In the case of ergot, the changes are seen usually after two to four months on the diet.

(5) Not only do vitamin A and carotene prevent the degenerative changes but even in affected animals, the improvement in the clinical condition on the addition of either of these substances to the diet is very great.

(6) The possible bearing of these results on convulsive ergotism, pellagra, lathyrism and the subacute combined degeneration in pernicious anæmia, tabes dorsalis, disseminateds clerosis and even on the malarial treatment of nervous syphilis is discussed.

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LESIONS OF THE CENTRAL NERVOUS SYSTEM CHARACTERISTIC OF PELLAGRA.

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THE autopsy was performed by Dr. William H. Snyder. The author wishes to express appreciation for his co-operation and aid in the study of the material.

INTRODUCTION.

Winkelman, in 1926, found 2,000 articles relating to the ætiology, clinical or pathological findings in pellagra. It is strange that with so much interest so little progress has been made in knowledge concerning this abnormality. Pellagra is commonly believed to be a deficiency disease; formerly it was considered to be due to eating spoiled maize, especially after this grain had been carried on an ocean voyage. Goldberger, in particular, has studied the relation of pellagra to food; Goldberger and Wheeler (1920) were able to produce symptoms of pellagra in white male convicts who submitted voluntarily to a restricted diet.

Clinically, the disease is characterized by four abnormalities; symmetrical skin lesions, sore tongue, diarrhœa and psychiatric or nervous manifestations. A history of restricted diet is usually obtained. An achylia gastrica is very often present; similar lack of free acid in the stomach is also present in other conditions associated with spinal cord damage, such as pernicious anæmia and carcinoma of the stomach. The relation of these different changes, one to the other, is not understood. The dermatologist might affirm, for example, that the primary abnormality was an increased sensitivity of the skin to light, so that lesions appeared on the exposed surfaces of the body. Toxins absorbed from the skin might then cause the irritation of the gastro-intestinal and central nervous systems. Or the neurologist might feel that the changes in the nervous system are primary, not only in the brain and spinal cord, but also in the autonomic cells scattered throughout the body. The injury of the autonomic cells would then be held responsible for the cutaneous and gastro-intestinal manifestations. Fascinating as it is to speculate in this way, there is no basis at the present time for such conjectures.

The lesions of the nervous system have been studied by many workers, and in order to understand the findings one fact must be borne in mind. The disease attacks the brain, cord and peripheral ganglia everywhere, so that the lesions are extremely diffuse. In most cases, however, one portion of the nervous system bears the brunt of the attack. If this is the cortex, the mental symptoms are most prominent; if the lateral and posterior tracts of the cord, the ataxia, paralysis and spasticity. For this reason all types of nervous and mental symptoms have been described, and all types of changes in the brain and cord. Individuals with pellagra often show marked remissions with accentuation of the disease during the spring months. The nervous and mental symptoms are not usually early developments, and are often absent during the first bout of diarrhœa and dermatitis.

All types of mental changes may be found in pellagra. Many of the early cases have symptoms typical of neurasthenia, and these individuals are often considered to have purely functional ailments. Melancholia with suicidal tendencies is very common, but excitements, stupor, mutism and delirium occur often. Epileptic attacks have frequently been observed; headaches may be extremely severe.

The neurological abnormalities also present great variations. There may be burning pain in the extremities with tenderness on palpation of the nerves. There often is a diminution of tactile, thermal and painful sensibility. The muscles show an increased response to excitation. Ataxia is often present in the legs and less frequently in the arms. There may be a positive Romberg's sign. Tremor occurs in the arms or legs, and is sometimes of the intention type. Dysphagia and dysarthria occur. The deep reflexes are frequently hyperactive and associated with extensor plantar responses, absent abdominal reflexes and clonus. Tremors and paralyses of the facial muscles have been described. The tongue may show a coarse tremor.

At autopsy the Italian pathologists have found changes in the meninges in practically all their cases. There is an opacity and thickening of the pia-arachnoid, usually diffuse but circumscribed in some of the cases. At times hæmorrhages or purulent exudates have been present in the arachnoid. There is sometimes œdema of the brain; marked atrophy of the cerebral convolutions has been noted.

Almost all workers agree that fatty and pigmentary changes may be observed in the small cerebral arterioles and capillaries, with hyalin deposits, particularly marked in the capillaries.

Fat or pigment deposits of an abnormal character are common in

the autonomic and sensory ganglia, but are present to a less degree in the cord, brain-stem, and in the cerebral cortex. The pigmentary changes occur in the cells of both the anterior and posterior columns of the cord; they are of the nature of pigmentary atrophy and are the expression of profound nutritional changes occurring in nerve cells. The abnormal pigment is not found in the nerve cells alone in pellagra, but also occurs in the cells of the heart, liver and spleen. Indeed, it has been stated that deposits of pigment in cardiac muscle are greater in pellagra than in any other disease.

The pigmentary changes are by no means the only abnormalities found in nerve cells. Alterations in the neurofibrils have been demonstrated, which are more marked in the large motor cells. Often the nucleus of the cell is eccentric, lying at the very edge of the cytoplasm. The nucleus may be atrophied or invisible, and the nucleolus stains with difficulty in many of the injured cells. Moreover, there is a loss of chromophilic granules in the nerve cells involved by this process; the granules are lost first from the central portion of the cytoplasm and later from the periphery.

Nerve fibres are altered even in the peripheral nerves. Many investigators have observed areas where the myelin sheaths had degenerated and free fat could be demonstrated in nerve trunks and in the cauda equina. All of the fibres appear to show a thinning of the myelin sheath.

The central canal of the cord is often obliterated, and there is an irregular proliferation of the ependymal cells. This is not characteristic of pellagra, but is present in many chronic toxic or infectious processes involving the spinal cord.

Wilson (1914) found granules in the neurolemmal cells of peripheral nerves which were stained violet with thionin. He called them π-granules and believed that they were increased in pellagra. It is known that neurolemmal cells round up and divide actively when the nerve fibres are injured.

In the spinal cord the fibres of the lateral, and less often of the posterior, columns bear the brunt of the injury. In many cases there is a pseudo-systematized degeneration of the antero-lateral columns. The condition does not differ radically from that found in primary anæmias, the so-called combined scleroses, except that the nerve cells are injured in pellagra. The lateral columns usually show the greatest injury in the thoracic portion of the cord, the posterior columns in the upper thoracic and cervical segments.

The posterior column changes resemble closely those found in tabes. There is, however, a maximal involvement at a different level in the spinal cord, for the posterior column involvement in tabes is more marked in the lumbar rather than in the thoracic segments. In tabes the root fibres are injured at the point where they enter the cord, while in pellagra the injurious agent attacks the whole primary sensory neurone, including the distal and proximal processes and the prolongation of the latter in the posterior columns. In pellagra the lateral pyramidal and the spino-cerebellar tracts in the lateral columns are also injured.

The cells of the posterior horns of the spinal cord often look quite normal in pellagra. In several cases the cells of Clarke's column have shown evidence of degeneration. The motor cells of the anterior horns exhibit changes which are present not only in the somatic motor but also in the autonomic cells.

There is no marked glial proliferation, but the areas where loss of cells or fibres have occurred are healed by glial overgrowth. There are often myelin bodies present in the sections of the cord stained with hæmatoxylin and eosin. Fat stains show droplets of fat either free or engulfed in phagocytic cells.

Similar changes may be found in the region of the brain-stem and cortex. Some brains show marked loss of cells and glial overgrowth; the changes are said to be most marked in the supragranular pyramidal layers.

The changes in the nervous system, in summary, are diffuse and are supposed to be of toxic origin. All portions of the neurones are involved, but some groups of cells are more often injured than others. Although the loss of nerve fibres in the tracts of the cord is diffuse, it often follows a definite pattern. The psychotic states are due to injury of the cortical neurones.

There are a few pathological changes in other portions of the body that may be mentioned. A general atrophy of all the striated musculature may occur. Similar atrophy involves the heart musculature and may be even more marked than in any other conditions. This has been related by some to disease of the cardiac autonomic cells, producing pigmentation and atrophy of the heart. There may be an involvement of the sympathetic cells, related to symptoms in the gastro-intestinal tract. Frequent inequality of the pupils may be explained upon a similar basis.

The question has arisen concerning the frequent association of

pellagra and tuberculosis. It is said that patients with pellagra are especially prone to develop tuberculosis, and particularly intestinal tuberculosis. This was true of three out of five cases in one series that was examined. A fourth case in this group showed healed lesions of the lung. In another group of fifteen cases, tuberculosis occurred nine times.

With this summary of previous work upon the subject, a case may be presented showing many clinical and pathological findings typical of pellagra. Particular stress will be placed upon the changes in the nervous system.

Case History, Clinical and Pathological Findings.

The patient, L. S. (J.H.H., unit 33389), was a white woman, aged 22, who was admitted to the Johns Hopkins Hospital, October 2, 1930. Only a meagre story of the illness could be obtained. The family history is of no significance. She is said to have been quite healthy until the beginning of the present trouble.

For three years previous to the present illness she had worked in a mill in Harrisburg, Pennsylvania. During this time the patient lived in a boarding house and nothing is known of her diet there. She returned to her home in Illsburg, Pa., in the fall of 1928 and remained well for two months. Then, in December, she had an illness which was diagnosed as influenza. She was very ill for a week and afterwards had a sore mouth. This trouble continued, and a few days later the patient developed a severe diarrhœa with five to ten stools a day, which persisted till she was admitted to the hospital.

Soon after the onset of the diarrhœa she developed a wet dermatitis which began on the backs of her hands, later appeared on her elbows, and still later on her knees. This dermatitis alternately dried and became wet to the time of her admission.

In June, 1929, she went to a clinic in Harrisburg and was told to take yeast. She did this for a week but stopped because it made her nauseated.

She had no nervous or mental symptoms until six weeks before coming to Baltimore. Then she became very nervous and irritable and showed some defects of memory. There was also drowsiness. The onset of the cerebral symptoms was rather acute. The nausea, vomiting and diarrhœa remained the same as it had been for eighteen months.

There seemed to be no dietary deficiency at home except that she ate little red meat.

On admission to the wards her temperature was 99·4° F., pulse 90, respirations 24, and the blood-pressure 110/80.

The patient was a tall, red-haired, very emaciated young woman. There was great weakness and she was obviously very ill. She seemed to be suffering pain in the region of the angle of the jaw and pointed to this area with her

finger. The patient was unable to make herself understood because of difficulty in articulation; she seemed to be conscious and to understand what was said to her. At times she was irrational.

The skin was pale and drawn. There was a dermatitis characterized by almost absolute symmetry. The lesions were yellowish-pink, rough, in some places cracked and scaly. Over both hands the skin was rough and over the knuckles bright pink. The dermatitis was further distributed; a small patch on the palmar surface of each wrist, over the olecranon on both elbows, about the external nares, on the point of the chin, on both knees in a crescent on either side of each patella, and over the feet and ankles in a boot-like distribution. Over the perineum and genitalia the skin was red and in areas excoriated, due possibly to soiling with fæces. There was a decubitus ulcer over the sacrum.

The tongue and buccal mucosæ were fiery red. Along the tongue margins and inside of cheeks were ulcers, covered with a grey film of exudate. The lingual papillæ were not atrophic.

The conjunctivæ were very pale. The pupils were equal, regular and responded to light and on accommodation; the extra-ocular movements were normally performed. The patient appeared to suffer from bright light. Ophthalmoscopic examination revealed no abnormalities.

The external auditory meatus was lined by very dry, scaly skin. Hearing was normal. The mucosa was infected and the teeth were extremely carious. The tonsils were moderately enlarged and covered by a thick, grey exudate. There was deep injection of the pharyngeal mucosa. The glands at the angles of the jaw and along the anterior border of the sterno-cleidomastoid muscle were large, firm, discrete and extremely tender.

The thorax was flat and there were deep hollows above and below the clavicles. The respiratory movements were somewhat laboured, shallow and showed occasional irregularities. The percussion note was normal over the whole chest. The breath sounds were rather harsh. A few moist râles were heard at the bases, posteriorly.

The heart was normal, but the first sound at the apex was rather rough and followed by a loud, blowing systolic murmur. The pulse was regular, of fair volume and quality. The vessel walls were not felt.

The abdomen was flat and showed fair muscle tone. There was no muscle spasm or rigidity. The liver, spleen and kidneys were not felt. There were no abnormal masses. No peristalsis or intestinal patterns could be seen. There was moderate tenderness in the left lower quadrant.

The patient seemed to suffer considerable pain. There was a thickness of speech that made it unintelligible. There was a constant tremor of the facial muscles and a coarse tremor of the hands. The deep reflexes in the arms were hyperactive and equal on the two sides. The knee- and ankle-jerks were extremely active and there was bilateral sustained ankle clonus. The plantar reflexes were flexor; the abdominal reflexes absent. There was no increased tonus in the extremities. Sensory examination was unsatisfactory.

The red blood-cells numbered four million; the hæmoglobin was 74 per cent. The white blood-count was 9,440 with a normal differential. The Wassermann reaction was negative. The non-protein nitrogen was 25 mg. per cent.

Examination of the stools revealed no blood and no parasites.

The presence of the symmetrical skin lesions, sore tongue, psychiatric and neurological abnormalities, combined with the diarrhœa, suggested that this was pellagra, although there was no history of dietary insufficiency.

The patient was placed on a 5,000 calories, liquid diet, rich in vitamins. She showed no response to treatment. Her condition grew gradually worse and she died six days after entering the hospital.

Autopsy.—The conditions found were as follows (Path. No. 11663).

On opening the abdomen a greatly enlarged stomach covered practically all the abdominal contents. The intestines were crowded low in the abdomen and pelvis; they seemed small and were of a greyish white colour. The spleen and liver appeared normal.

The surface of the left lung was covered with dense adhesions of a stringy, tough, elastic nature, which held it firmly to the chest wall, diaphragm and pericardial sac. The left lung was free from adhesions and the pleural and pericardial surfaces were smooth.

The heart was small and its surface was smooth; the valves seemed delicate, although the mitral was a little thickened along its margin.

Both lungs showed the effect of aspiration of gastric contents. The left lung presented a number of caseous nodules, scattered throughout both upper and lower lobes. The bronchus was lined with necrotic material, evidently the result of aspiration. The bronchial nodes were quite small. Throughout the lung the lesions gave the suggestion of being related closely to the lumen of the bronchus.

In the lesser curvature of the stomach there was an area about 3 cm. in diameter, quite near the cardiac orifice, which was smooth and white. On section, the mucosa was found to give place suddenly to a scar-like patch which suggested an old, healed ulcer. There were some rugged ulcers in the lower part of the ileum with induration of their wall. In the colon, just past the ileo-cæcal valve, there were a number of shallow, rather ragged ulcers.

The liver showed no marked abnormality. The kidneys looked normal with smooth surfaces and normal striations. The aorta was delicate and elastic with only a little fat deposit. The uterus was extremely small. The bone-marrow of the femur was aplastic.

The meninges of the spinal cord and brain seemed somewhat thickened. No lesions visible to the unaided eye were visible in sections of the brain and spinal cord.

Microscopic study reveals relatively few abnormalities outside of the nervous system.

Sections of skin from the lesions on the hand, ankle and thigh were studied. There was a thickening of the corium over all these areas but no marked

exfoliation. A moderate lymphocytic infiltration of the deep layers was present. The stratum germinativum was intact and of normal appearance everywhere. Elastic tissue stains revealed no further abnormalities.

In the heart there were a few small hæmorrhages between the muscle bundles. All the muscle fibres presented slight atrophy but no increase in pigment was present.

Sections of the left lung revealed many small tubercles with giant cells. The bronchi were filled with homogeneous pink-staining material infiltrated with leucocytes. Sections of the right lung showed the same material in the bronchi and alveoli, and some necrosis of the lung tissue. No tubercles were found in the right lung. A left bronchial lymph node was necrotic and contained numerous tubercles with giant cells.

There were numerous tuberculous ulcers in the colon extending down into the submucosa.

The thyroid was normal, except that the collagen in the alveoli was somewhat shrunken.

Sections of the stomach, liver, pancreas, spleen, kidneys, adrenals and ovaries revealed no abnormalities.

Sections of nerve trunks and of the nerve roots in the cauda equina appeared normal in sections stained with hæmatoxylin or with thionin. The neurolemmal cells, however, in places looked more numerous and rounder than normal, and the pink π-granules, described by Wilson, could be seen in the cytoplasm of these cells in sections stained with thionin. Fat stains of the nerves showed many droplets of free fat scattered in small groups among the nerve fibres.

The pia-arachnoid of the spinal cord and brain was very little thickened. Frozen sections of the spinal cord, stained for fat, revealed considerable neutral fat in the lateral columns in the position of the spino-cerebellar and lateral pyramidal tracts. This fat was present as free droplets and also in phagocytic cells which were most common around the walls of the small blood-vessels (fig. 2). Similar phagocytic cells were grouped in the arachnoid. Sections stained by the Spielmeyer method for myelin sheaths confirmed the finding of destruction of fibres, inasmuch as there was a considerable decrease in the number of myelinated fibres in the lateral column (fig. 1). The picture as seen with this stain was rather characteristic, inasmuch as there was no complete destruction of tracts or groups of fibres, but a general thinning out and decrease in the numbers. No involvement of the posterior or anterior columns was present. The lesions in the lateral columns were most marked in the upper thoracic and cervical portions of the cord, but they could also be demonstrated in the lumbar and sacral segments.

There was a general increase in the amount of lipoid pigment in the cytoplasm of all the nerve cells. This was greatest in the cells of the autonomic and sensory ganglia (figs 3 to 5), and of smaller amount in the cells of the central nervous system. The large motor cells of the cord contained considerable pigment (fig. 7). In the sensory ganglia the smaller sensory cells

showed the greatest accumulation of pigment (figs 3 to 5). This was collected in the centre of the cytoplasm and the nuclei of the cells were markedly displaced. In the motor cells the pigmentation was near the edge of the cytoplasm, often at the base of the principal dendrite.

Many nerve cells presented evidence of severe injury: this was also true of those in the autonomic and sensory ganglia. There was often marked chromatolysis and the nucleus was displaced, as has been described. Certain cells were in the final stages of disintegration. In the cord the cells of the dorsal nucleus of Clarke (fig. 6) were the most markedly abnormal: the nuclei had crenated margins and were placed at the edge of the cytoplasm, considerable pigment was present and the chromophilic granules were very few in number. The changes in Clarke's nuclei are particularly interesting, in that these cells give rise to a portion of the spino-cerebellar fibres.

The motor cells in the ventral columns of the cord were in general normal, except for a much greater pigmentation than is found in healthy young people The motor cells in the medulla were more severely damaged and many cells in the facial and vagus nuclei showed chromatolysis. This explains the facial tremors and dysarthria observed in the patient.

No visible abnormalities were observed in sections of the cerebral cortex that would account for the mental symptoms.

The blood-vessels of the nervous system appeared normal, and there was no thickening or hyalinization of the vessel walls which has been described in cases of pellagra.

Discussion.

The patient showed the typical clinical findings of pellagra. A history of dietary insufficiency was not obtained, but no really adequate story could be elicited. Post-mortem examination revealed tuberculosis of the lungs and tuberculous ulcers of the bowel. The question naturally arises as to whether all the abnormalities may be explained upon the basis of the tuberculosis. Is pellagra a definite entity or group of symptoms which may be produced by several ætiological agents? Certainly the relation of diet to the disease is not yet entirely clear, for the results of feeding experiments upon rats cannot be applied directly to human problems. The only real proof of pellagra as a deficiency disease rests on the experiments of Goldberger and Wheeler on white convicts. There is another aspect to this problem. In cases of severe diarrhœa the patient may not be able to extract adequate substances from the diet to maintain a proper metabolism, and the remaining abnormalities may follow. For these reasons the tuberculous infection of the bowel cannot be lightly dismissed. Although tuberculous ulcers have been found frequently in patients who were supposed to die of pellagra, this does not affect the underlying question.

It was unfortunate that the patient was so ill on entrance to the hospital that the neurological examination was necessarily inadequate. There was delirium, and speech was unintelligible. A coarse tremor was noticed in the hands and in the facial muscles. The knee- and ankle-jerks were increased and there was ankle clonus. The abdominal reflexes were absent. It is interesting that the findings at autopsy may be correlated with the involvement of the spino-cerebellar and pyramidal tracts.

The neurological symptoms had been present for only a few weeks, and the lesions in the lateral columns of the cord were comparatively fresh. Thus fat was found in droplets and included in phagocytic cells.

The accumulation of pigment in the nerve cells was much greater than one would expect in an individual of this age. The cells of the autonomic and sensory ganglia showed the most marked pigment changes. In the spinal ganglia the smaller cells contained huge accumulations of pigment in the central portions of the cytoplasm. Since the spino-cerebellar tracts were the most involved, it is suggested that these cells are the primary sensory neurones of the spino-cerebellar pathway. It is unfortunate that no sensory examination could be made in this case. The dorsal column cells of Clarke showed marked degeneration. However, most of the cells in the anterior and posterior horns of the cord looked quite normal. There was some increase in pigment in the large, somatic motor cells.

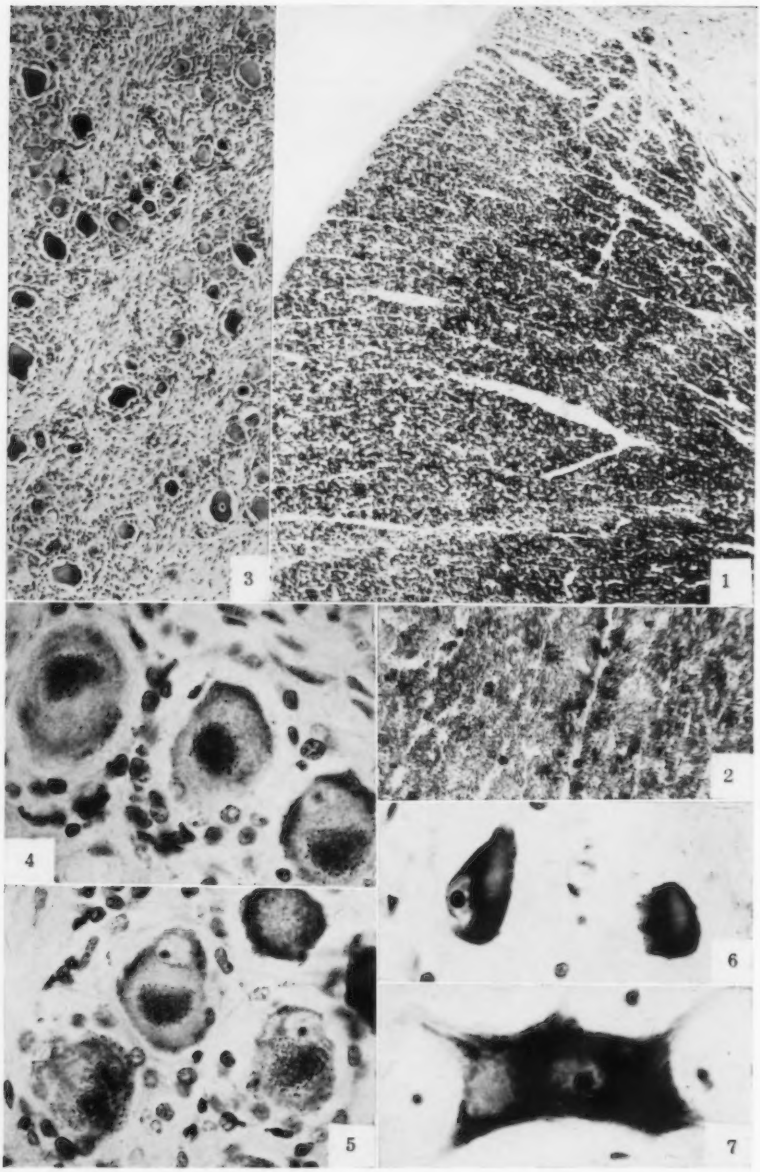
Two other pathological findings are worthy of note. The heart was extremely small and its fibres were atrophied. The uterus was also small and infantile. The small size of the heart in patients with pellagra has been frequently observed. It is probable that the small uterus is to be explained on the basis of the same underlying factor.

Summary.

The patient, a white woman of 22, had symmetrical skin lesions, sore tongue, diarrhœa, mental and neurological symptoms characteristic of pellagra. There was no history of dietary insufficiency.

Histological study of the central nervous system revealed changes which have been considered typical of this disease. These abnormalities were extremely diffuse and involved all portions of the neurones. Accumulations of pigment were found in cells of the sensory and autonomic ganglia and those in the spinal cord and brain-stem. The antero-lateral columns of the cord were most severely

PLATE VII.



To illustrate paper by Orthello R. Langworthy.

involved; there was no abnormality in the posterior columns. The lesions involved particularly the spino-cerebellar and cortico-spinal tracts. It is probable that the neurological abnormalities were of only short duration; considerable fat could be demonstrated in the lateral columns of the cord.

The small cells of the sensory ganglia showed the greatest deposit of pigment. It is suggested that these cells are the primary neurones of the spino-cerebellar pathway.

DESCRIPTION OF FIGURES.

PLATE VII.

FIG. 1.—Section of the spinal cord in the thoracic region stained by the Weigert-Pal method. Only one lateral column is shown. It will be noticed that there is a distinct thinning of the number of medullated fibres at the edge of the cord in the region of the spino-cerebellar fibres and a smaller loss of fibres from the cortico-spinal tract.

FIG. 2.—In the areas that showed a decrease of medullated fibres in fig. 1 considerable fat could be demonstrated in frozen sections. Some of this fat was present as free droplets; the remainder was present in phagocytic cells which were particularly numerous around the small blood-vessels. This picture is in poor focus due to the thickness of the section. It does show fatty droplets and deeply staining phagocytic cells around the vessel wall.

FIG. 3.—Photomicrograph of the cells in a posterior root ganglion; the section was stained with thionin. The small cells in the upper centre show large collections of pigment in the central portion of the cytoplasm. Other cells show various stages of degeneration.

FIGS. 4 and 5.—High power photomicrographs of some of the smaller cells of a posterior root ganglion which show such marked pigment accumulations. The nuclei of two cells in fig. 5 are pushed to the edge of the cytoplasm The centre of the cytoplasm in all these cells is filled with a large mass of lipochrome pigment.

FIG. 6.—Degenerated cells of the dorsal nucleus of Clarke stained with thionin. The axones from these cells are spino-cerebellar fibres. Both nuclei are at the edge of the cells and the central portion of the cytoplasm contains pigment. The cell on the right appears to be disintegrating.

FIG. 7.—Less marked changes were found in the anterior horn cells of the spinal cord. There was an excess of pigment in the cytoplasm which is shown in this photomicrograph.

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THE EQUILIBRIUM BETWEEN CEREBROSPINAL FLUID AND BLOOD-PLASMA.

V.—The Osmotic Pressure (Freezing-Point Depression) of Human Cerebrospinal Fluid and Blood-serum.[1]

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Mestrezat [1], 1912, determined depression of the freezing-point of the cerebrospinal fluid on five fasting normal subjects. These were patients who were about to be operated on under spinal anæsthesia, for hernia (three cases), varices (one case), and tumour of the leg (one case). The values obtained were $-0{\cdot}57^{\circ}$ C. in three cases, $-0{\cdot}58^{\circ}$ and $-0{\cdot}59^{\circ}$ C. in one case each. The value of the freezing-point of a mixture of twenty similar normal fluids was $-0{\cdot}577^{\circ}$ C.

Mestrezat did not make comparative determinations on the serum of these cases, but called attention to the fact that these values for cerebrospinal fluid are essentially the same as the average normal value for the freezing-point depression of the human serum. In the earlier literature, which was reviewed by Mestrezat [1], there is almost no reliable data on the freezing-point of normal cerebrospinal fluid, and none where it is compared directly to serum.

Depisch and Richter-Quittner [2] measured the freezing-point of cerebrospinal fluid and blood-serum in twenty-three patients. In only two of these cases was the spinal fluid normal. With one exception, Depisch and Richter-Quittner found the freezing-point depression of the spinal fluid greater than that of the serum. It is not stated whether these patients were fasting or not at the time the samples were obtained. They used the micro-method of Burian and Drucker [3], which may account for the discrepancy between their results and ours.

Teschler [4] is the only other author to give comparative data on the freezing-point of the cerebrospinal fluid and the serum in a series of cases. In a total of forty-three such determinations the freezing-point of the serum was the same as that of the cerebrospinal fluid within $0{\cdot}005^{\circ}$ in twenty cases. In the six "normal" cases only once did the freezing-points of serum and cerebrospinal fluid fail to agree within $0{\cdot}005^{\circ}$.

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Teschler used a Beckmann thermometer. He does not state whether his patients were fasting or not. He concluded that the freezing-point of the cerebrospinal fluid is the same as that of the serum within the limits of error of the determination.

In this paper we report comparative freezing-point determinations on simultaneous samples of blood-serum and cerebrospinal fluid in ninety-four instances (on seventy-three patients).[1] These are shown in Tables I, II, III and IV. Twenty-three of these determinations on eight patients were in cases of various kinds of meningitis. Sixty-five of the non-meningitic cases and nine of the cases with meningitis were fasting nine hours, or more, before the samples of cerebrospinal fluid and blood were obtained.

The Beckmann apparatus was used exactly as described in Findlay's textbook [7], a Heidenhain thermometer being substituted for the Beckmann thermometer. Both serum and spinal fluid were collected under oil and kept on ice until the determinations were made. Determinations were started within half an hour of obtaining samples, that of spinal fluid usually being done first and the serum immediately afterwards. Three or more freezing-points were determined on each sample, the average figure for the three being given. In the vast majority of cases these three determinations did not vary more than 0·005°. The freezing-point of distilled water was determined at frequent intervals, usually on the day of each experiment. The temperature of the cooling bath was never more than 3° below the freezing-point. Super-cooling was kept at a minimum not exceeding half a degree. Seeding was done with a minute crystal of snow from that condensed on the sides of the glass jar containing the freezing mixture. Both the freezing mixture and the solution to be frozen were stirred by an electric device, at a uniform rate.

No stem correction was made. This error should be the same for serum and cerebrospinal fluid, as the room temperature rarely varied during the course of the determinations. No effort was made to correct for losses of carbon dioxide to the atmosphere after the samples were taken from under oil and placed in the freezing chamber.

Since the known errors in the method should be approximately the same for both serum and cerebrospinal fluid, we believe our data are significant for a comparison of the freezing-point of blood-serum with that of the cerebrospinal fluid.

[1] Complete details of the examination of the blood-serum and spinal fluid in most of these cases may be found under the same case numbers in papers I and II of this series (V) and (VI).

Results.

In forty-four of the seventy-one comparative determinations in non-meningitis cases, the freezing-point of the cerebrospinal fluid was the same as that of the serum within 0·005°. In only fifteen instances was the difference in freezing-point depression greater than 0·015°, the greatest difference being 0·037° (Case 220).

This indicates that the human cerebrospinal fluid is ordinarily in osmotic equilibrium with the blood-serum, and confirms the views of Mestrezat and Teschler. Occasionally, however, appreciable differences in freezing-point depression of these two fluids may occur. This is probably to be explained by the latent period before changes in composition of the blood are reflected in the lumbar cerebrospinal fluid. Ventricular fluid might be expected to reflect such changes with much greater rapidity.

Even in the cases of acute purulent and tuberculous meningitis (Table IV) where one would expect fever, sweating and vomiting to produce rapid changes in the composition of the blood, six of our twenty-three comparative determinations showed identical freezing-points within 0·005° C. while in only ten instances was the freezing-point difference between blood-serum and cerebrospinal fluid greater than 0·025° C. In each of these ten instances, moreover, the blood-serum was hypertonic to the spinal fluid, which is what one would expect if the patient were being rapidly dehydrated by sweating and vomiting and the spinal fluid had not reached equilibrium with the concentrated blood.

The spinal fluid in these cases of meningitis showed a distinct tendency to have a lower osmotic pressure than normal. In fifteen instances the freezing-point depression was less than 0·545° C. while in only four instances was it greater than 0·570° C. This tendency had been previously noted by Mestrezat [1]. The blood-serum was much more variable, in six instances having an osmotic pressure below normal, and in ten instances an osmotic pressure above normal. The extremely high serum value in Case 338 we are unable to explain. As the chlorides, non-protein nitrogen, and sugar on the same sample of serum were within normal limits the figure may be in error.

As we have pointed out previously [8, 9, 10] both serum and spinal fluid chlorides fall rapidly at the onset of meningitis as they do also in all acute febrile diseases. We believe this is the cause of the low osmotic pressure of the spinal fluid in meningitis. Whether this hypotonicity is still present in the blood at the time of lumbar puncture probably depends upon the degree of subsequent dehydration.

We have previously reported [11, 12, 13], that whereas water drinking is normally followed by only minor changes in the composition of the blood-serum, when the water is taken during a rising temperature or during the anti-diuretic action of posterior pituitary lobe extract, an appreciable dilution of the blood-serum takes place and this dilution is reflected in the cerebrospinal fluid. Table V shows this effect during typhoid vaccine fever (five cases), and Table VI during the anti-diuretic action of posterior pituitary extract ("vasopressin"[1]) (nine cases). The "vasopressin" was given by subcutaneous injection.

It will be seen in these cases that such experimentally induced dilution of the blood-serum is reflected in the cerebrospinal fluid and that these two fluids tend to remain in osmotic equilibrium.

Discussion.

In two previous communications [14, 15], one of us (F.-S.) has reviewed the literature and has discussed the nature of the cerebrospinal fluid and the basis for considering it a dialysate in osmotic and hydrostatic equilibrium with the blood plasma. Thus it has been shown that the cerebrospinal fluid pressure may be varied at will either by varying the intracranial venous pressure [16] or by varying the osmotic pressure of the blood [17]. That the cerebrospinal fluid is formed largely from the choroid plexus is established both by the experiments of Dandy [18] and by the direct observations of Schaltenbrand and Putnam [19]. Moreover, Foley was able to reverse the flow of cerebrospinal fluid through the choroid plexus [20] and this one of us (F.-S.) has confirmed [21].

It remained to show that the cerebrospinal fluid had the same total osmotic pressure as the blood plasma, and to demonstrate that experimentally induced changes in the latter are reflected in the former. These results we are now reporting.

Such accumulative evidence from various angles leaves little room for doubt that the cerebrospinal fluid is a dialysate in equilibrium with the blood plasma.

Summary.

In seventy-one comparative determinations of freezing-point depression of human blood-serum and cerebrospinal fluid in non-meningitic cases, the results were identical within the error of the method in over

[1] Courtesy of Parke, Davis Company.

60 per cent. of the cases. In 80 per cent. the difference in freezing-point depression was less than 0·016 C.

Experimentally induced dilution of the blood-serum by water drinking during a rising fever or during the anti-diuretic action of posterior pituitary lobe extract is reflected by a similar dilution in the cerebrospinal fluid.

Conclusion.

The cerebrospinal fluid is a dialysate in osmotic equilibrium with the blood plasma.

Table I.—Cases with Normal Cerebrospinal Fluid.

Case No.		Freezing-point —° C. Serum	C.S.fl. Fl.
1	..	0·577	0·573
2	..	0·549	0·548
3	..	0·580	0·577
4	..	0·568	0·567
5	..	0·559	0·559
6	..	0·556	0·558
7	..	0·570	0·568
8	..	0·580	0·578
9	..	0·588	0·586
10	..	0·582	0·581
11	..	0·566	0·565
12	..	0·576	0·578
23	..	0·549	0·551
24	..	0·557	0·559
25	..	0·589	0·589
26	..	0·550	0·549
27	..	0·560	0·555
28	..	0·542	0·541
38	..	0·565	0·567
46	..	0·583	0·561
48	..	0·538	0·559
50	..	0·572	0·584
51	..	0·593	0·576
52	..	0·588	0·563
56	..	0·583	0·575
57	..	0·543	0·550
79*	..	0·568	0·571
119	..	0·584	0·570
123	..	0·577	0·557
126	..	0·578	0·583
157	..	0·537	0·538
160	..	0·561	0·574
187	..	0·536	0·537
329*	..	0·581	0·558
336	..	0·559	0·558
High	..	0·593	0·589
Low	..	0·536	0·537
Average	..	0·567	0·565

* Patients fasting less than nine hours.

TABLE II.—CASES WITH SLIGHT ABNORMALITIES IN CEREBROSPINAL FLUID.

Case No.		Freezing-point —° C. Serum	C.Sp. Fl.
39	..	0·582	0·584
40	..	0·567	0·563
41	..	0·575	0·573
42	..	0·571	0·573
43	..	0·560	0·563
44	..	0·563	0·561
45	..	0·577	0·560
47	..	0·599	0·576
49	..	0·600	0·575
53	..	0·590	0·567
54	..	0·582	0·563
55	..	0·582	0·568
58	..	0·576	0·585
59	..	0·589	0·567
73	..	0·590	0·590
326	..	0·577	0·574
96*	..	0·557	0·558
121	..	0·535	0·538
219	..	0·534	0·534
220	..	0·608	0·571
222*	..	0·596	0·597
High	..	0·608	0·597
Low	..	0·534	0·534
Average	..	0·577	0·568

* Patients fasting less than nine hours.

TABLE III.—CASES WITH ABNORMAL CEREBROSPINAL FLUID.

Case No.		Freezing-point —° C. Serum	C.Sp. Fl.
74	..	0·583	0·575
75	..	0·567	0·580
76	..	0·538	0·540
77	..	0·598	0·603
78	..	0·579	0·579
115*	..	0·570	0·555
175	..	0·564	0·570
208*	..	0·548	0·539
215	..	0·538	0·561
325	..	0·578	0·583
340	..	0·604	0·575
341	..	0·563	0·566
342	..	0·552	0·551
343	..	0·636	0·633
344	..	0·570	0·572
High	..	0·636	0·633
Low	..	0·538	0·539
Average	..	0·573	0·572

* Patients fasting less than nine hours.

TABLE IV.—CASES WITH ACUTE PURULENT AND TUBERCULOUS MENINGITIS.

Acute Purulent Meningitis.

Case No.		Freezing-point −.° C. Serum	C.Sp. Fl.
272	..	0·524	0·526
273	..	0·555	0·527
278*	..	0·616	0·607
279	..	0·576	0·580
280	..	0·576	0·583
288*	..	0·501	0·490
290	..	0·535	0·490
298*	..	0·546	0·540
300*	..	0·537	0·532
301*	..	0·570	0·541
302*	..	0·595	0·557
303*	..	0·629	0·542
304*	..	0·634	0·542
305*	..	0·577	0·577
306*	..	0·552	0·528
307*	..	0·580	0·541
308*	..	0·562	0·557
309*	..	0·567	0·547

Tuberculous Meningitis.

233	..	0·591	0·546
337	..	0·512	0·507
338	..	0·726	0·510
339	..	0·561	0·518
265*	..	0·525	0·519
High	..	0·726	0·607
Low	..	0·501	0·490
Average	..	0·571	0·539

* Patients fasting less than nine hours.

TABLE V.—THE EFFECT OF WATER DRINKING DURING THE ANTI-DIURETIC ACTION OF TYPHOID VACCINE FEVER UPON THE FREEZING-POINT DEPRESSION OF THE BLOOD-SERUM AND THE CEREBROSPINAL FLUID.

Case No.	Time of first sample	Freezing-point depression (−.° C.)	Time of injection of typhoid vaccine	Dose (millions bacteria)	Water ingested in interval (c.c.)	Urine output (c.c.)	Time of second sample	Freezing-point depression (−.° C.)	Change in freezing-point °C.
11	Serum A.M. 9.50	0·566	A.M. 1·48	250	200	?	P.M. 8	0·560	— 0·006
	C.S.F. 10.41	0·564					8·55	0·560	— 0·004
23	Serum 10	0·549	11·35	50	360	?	3·40	0·541	— 0·008
	C.S.F. 11	0·551					4·05	0·544	— 0·007
24	Serum 10.30	0·557	10·45	50	1,200	?	4·07	0·543	— 0·014
	C.S.F. 11	0·559					4·40	0·552	— 0·007
28	Serum 10.10	0·542	11·53	200	1,320	325	4·44	0·531	— 0·011
	C.S.F. 11.10	0·541					5·12	0·533	— 0·008
57	Serum 9.51	0·543	11	125	1,450	?	4·20	0·531	— 0·012
	C.S.F. 10.35	0·550					4·51	0·542	— 0·008

TABLE VI.—THE EFFECT OF WATER DRINKING DURING THE ANTIDIURETIC ACTION OF POSTERIOR LOBE PITUITARY EXTRACT (VASOPRESSIN), UPON THE FREEZING-POINT DEPRESSION OF THE BLOOD-SERUM AND THE CEREBROSPINAL FLUID.

Case No.	Time of first sample	Freezing-point depression	Time of injection of vasopressin	Dosage (c.c.)	Water ingested in interval (c.c.)	Urine output (c.c.)	Time of second sample	Freezing-point depression	Change in freezing-point °C.
			A.M.				P.M.		
4	Serum 10.20	0·568	11.45	0·50	1,800	300	3.07	0·543	— 0·025
	C.S.F. 11.10	0·567					2.50	0·570	+ 0·003
75	Serum 9.40	0·567	10.06	0·50	2,000	270	3	0·549	— 0·018
	C.S.F. 10	0·580					2.50	0 553	— 0·027
53	Serum 9.55	0·590	10.45	0·50	2,200	0	2	0·565	— 0·025
	C.S.F. 10.20	0·567					2	0·556	— 0 011
47	Serum 10	0·599	12.05	0·50	2,125	310	3.20	0·581	— 0·018
	C.S.F. 10.20	0·576					3.25	0·577	+ 0·001
41	Serum 12.07	0·575	12.09	0·25	3,000	235	3.23	0·541	— 0·034
	C.S.F. 12.17	0·573					3.25	0·561	— 0·012
126	Serum 9.32	0·578	10.35	0·50	3,350	0	2	0·541	— 0 037
	C.S.F. 10.30	0·583					1.45	0·565	— 0·018
78	Serum 9.30	0·579	11.15	0·50	3,350	450	3.13	0·520	— 0·059
	C.S.F. 11.05	0·579					3.30	0·528	— 0·051
119	Serum 9.55	0·584	11.15	0·50	3,685	522	2.50	0·553	— 0·031
	C.S.F. 10.40	0·570					2.46	0·558	— 0·012
59	Serum 9.55	0·589	10.55	0·50	4,020	680	3.45	0.542	— 0·047
	C.S.F. 10.53	0·567					3.20	0·541	— 0·026

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PARATHYROID TETANY IN DOGS, AND ITS ABOLITION BY CURARE.

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In the course of an investigation of the neurological mechanism concerned in the production of tetany, it was considered of importance to reconsider the effect of giving curare in this disease. That the poisonous action of curare is a peripheral one was established by the experiments of Claude Bernard [1] and Kolliker [2]. Evidence that the site of this action was a myoneural junction, and not the end-plate of the motor nerve, was first brought forward by Langley [3]. More recently, Lapicque [4] has considered the drug to produce a difference between the chronaxies of the motor nerve and of the muscle fibres by lengthening that of the latter. The action of curare in removing the muscle spasm of tetany has been recorded by various observers [5].

In our experiments, the thyroid—and their included parathyroid—glands were removed from a series of fourteen dogs, with resulting active tetany in twelve. Fits occurred in about two days after the operation, the limits being twenty-four and sixty-eight hours in this series.

Appearance of Dogs in Tetany.

At the onset of the attack the dog appears to be in a shivering fit. It lies curled up, trembles and when disturbed will stand apathetically, with occasional clonic jerks or fibrillary tremors in various muscles of the body. Shortly afterwards, the animal lies upon its side, with outstretched legs and extended head. Increased tone in the muscles of the limbs is usually present from the first onset of the genuine spasms of tetany.

The latter consist of tonic, clonic and fibrillary muscular contractions. Though extensor tone is invariably increased, tonic fits are not always present. When they are, they are very striking. Uninterrupted rigidity occurs, and it is of such a degree that the limbs are flexed with great difficulty by the observer. The spasm may persist for hours unchanged. The limbs are chiefly affected, but some opisthotonus is frequently shown. The clonic convulsions may be superimposed upon some degree of tonic spasm; often they are found alone. They consist

of violent shock-like contractions of isolated muscles or groups of muscles, notably in the scalp, limbs and spinal muscles. Fibrillary twitches of small groups of muscle fibres are found coincident with the other elements of tetany, or as its sole manifestation.

Electrical Reactions.

Electrical reactions were taken by a simple technique [10] and were found to be a valuable and constant index of latent or active tetany. Increased excitability to galvanic stimulation occurred on the supervention of tetany, though the threshold varied considerably among normal dogs at different times, as the following table shows :—

Variations in Electrical Reactions. (Highest and Lowest Record in 3 normal Dogs.)

Dog	1	2	3
K.C.C. ..	0·5-1·2 ma. ..	0·85-1·5 ma. ..	0·25 -0·85 ma.
K.O.C. ..	5·0-5·0 ..	5·0 -7·5 ..	1·2 -3·0
A.C.C. ..	1·8-2·2 ..	2·2 -3·5 ..	0·475-1·0
A.O.C. ..	1·4-2·2 ..	1·2 -3·5 ..	0·625-1·0

An example of the gross change on the onset of tetany is as :—

Dog 5	Normal	Tetany
K.C.C ..	1·2 ma. ..	0·28 ma.
K.O.C. ..	5·0, 7·5 ..	0·7
A.C.C. ..	2·2 ..	0·55
A.O.C. ..	1·6 ..	0·17

With the exception of the kathode opening current (K.O.C.), the electrical reactions of one normal dog may be as low as, or lower than, those of another dog in tetany, though this is exceptional.

	Lowest normal (Dog 7)	Active tetany (Dog 6)
K.C.C. ..	0·25 ..	0·4
K.O.C. ..	1·2 ..	0·4
A.C.C. ..	0·43 ..	0·8
A.O.C. ..	0·63 ..	0·5

We obtained none of the grossly irregular and unpredictable relationships between the various forms of galvanic stimulus recorded by Paton and his co-workers [6]. Far the most constant and valuable indicator of electrical hyper-excitability, such as occurs in tetany, is the kathodal opening contraction (K.O.C.), and this is the criterion used in this paper. By K.O.C. is meant the minimal current in milliamperes which will excite a contraction of a muscle when the flow of the current is interrupted. In tetany K.O.C. is characteristically reduced to about one-tenth its normal value. In spite of the wide variations among normal dogs, we

found no overlap between the readings of tetany and of normal excitability. A normal reading of under 1·0 ma. was quite exceptional in any dog, while a reading over 0·70 ma. was not found in any dog in active tetany. A reading of 0·5 ma. or under was a definite indication of tetany.

With regard to the other galvanic stimuli, we found the kathodal closing current (K.C.C.) threshold little worthy of reliance as a criterion of the form of excitability we were measuring. This is in agreement with the findings of Thiemich and Mann [8] in children. Von Pirquet [9] refers to anodal hyper-sensitivity being greater than kathodal in tetany, and this we confirmed. A.C.C. and A.O.C. frequently fell respectively to one-quarter and one-tenth normal.

Characteristic readings are :—

	Normal	Tetany
A.C.C. ..	1·62 ma. ..	0·68 ma.
A.O.C. ..	3·50 ..	0·37

We did not, however, find anodal readings as constant or reliable as kathodal. The order of sensitivity of the forms of stimulation is of little value as a criterion of hyper-sensitivity, with the possible exception of the frequent fall of A.O.C. below A.C.C. in tetany. Very occasionally A.O.C. was found to indicate latent tetany more readily than K.O.C., and for this reason the anodal reaction was always recorded.

The Administration of Curare.

General observations.—The dogs used were of mixed breeds, most being mongrel spaniels or terriers of weights between 20 and 26 lb. Fourteen dogs were used in all. Curare was given to eight dogs in tetany and to six normal dogs. The curare—Messrs. Burroughs Wellcome's tablet preparation—was a resinous substance of somewhat poor solubility in warm saline, and it was not possible to ensure a constant rate of absorption when injected subcutaneously. Accurate dosage per kilogram of body-weight was not attempted, but the initial dose of 86·4 mg. was based upon a dose of 8·6 mg. per kilo approximating to that used by other workers. This dose killed the first dog in thirty-five minutes, having abolished violent tonic tetany of four hours' duration in twenty minutes; 54·0 mg. subsequently killed a normal dog in forty-five minutes.

Reduction of the dose abolished the spasm of tetany without consequent death or even obvious paralysis. Two examples will be quoted.

Dog 4.—Summary.

Tetany followed thyroidectomy in twenty-four hours. The condition was one of tonic extensor rigidity of all four limbs, with superadded clonic contractions of the scalp and fibrillary tremors of limb and trunk muscles.

Tetany was observed continuously for twenty minutes. It was extremely severe and underwent no modifications. Curare (21·6 mg.) was then given subcutaneously, in one dose. The dog was unconscious.

Results.

In thirteen minutes the tonic spasm of the legs was much diminished.

In fifteen minutes the natural flaccidity of the limbs was restored, but clonic and fibrillary movements continued.

In twenty-five minutes there was complete cessation of clonic and fibrillary movements. The dog took notice.

Flaccidity remained for four hours, with the exception of slight rigidity at intervals after the first two hours.

Clonic and fibrillary twitches returned momentarily from time to time.

Voluntary movements of the limbs and head commenced at one hour after the abolition of the spasm, and within four hours the dog had leapt off the table and walked shakily across the floor.

Dog 5.—Summary.

Tetany consisted throughout of clonic muscular spasms varying in degree from fibrillation of a few muscle fibres to shock-like contractions of large muscle groups. In the latter class the contractions appeared sometimes to be single, isochronous jerks of the muscle group at about one-second intervals.

At other times the jerk was made up of half a dozen or more very rapid isolated contractions, of the speed of a roll of a kettle-drum. Sometimes one massive group contraction was many times repeated (e.g., extension of the hind limb). At no time was tonic spasm or great spasticity observed. The walk was spastic and ataxic. In addition the limbs seemed weak. Laryngeal spasm was present.

Tetany was observed intermittently for one hour, and continuously for twenty minutes. Whilst varying in degree, it was never absent for more than a moment. Bouts of maximum severity were becoming

more frequent and more severe, when the first dose of curare was given.

Curare (21·6 mg.) was given subcutaneously in two doses, separated by fifteen minutes interval. No diminution of tetany occurred between the doses.

Results.

In six minutes jerking of the limbs became very slight. Laryngeal spasm continued.

In ten minutes laryngeal spasm and tetany both vanished completely.

In fifteen minutes the dog walked, ran and wagged his tail. He seemed a little tired, but showed no signs of paresis.

In twenty-five minutes the electrical reactions still showed latent tetany.

In thirty-five minutes occasional twitches of one limb returned.

In fifty minutes clonic tetany and laryngismus were brought on by exercise. Both were relieved in two minutes by rest and oxygen inhalations.

Dosage of Curare.

In our first series of dogs in tetany, the results of giving curare were as under :—

Dog	Dose of curare	Tetany abolished in	Paralysis
2	86·4 mg.	15 mins.	Present (death 20 mins. later)
3	43·2 ,,	25 ,,	Present (death 55 mins. later)
4	21·6 ,,	25 ,,	Present (recovered)
5	21·7 ,, 10·8 ,,	25-35 ,,	Absent
6	27·0 ,,	25-35 ,,	,,
7	21·6 ,,	25-35 ,,	,,
8	27·0 ,,	25-35 ,,	,,
9	16·2 ,,	25-35 ,,	,,
10	27·0 ,,	25-35 ,,	,,

We then found a margin between the dose which would remove tetany and that required to produce paralysis.

Dog	Dose abolishing tetany	A dose which failed to produce paralysis
5	10·8 mg.	16·2 mg.
6	21·6 ,,	37·9 ,,
9	16·2 ,,	27·0 ,,
10	27·0 ,,	40·5 ,,

Electrical Reactions with Parathormone and Curare.

In tetany abolished by parathormone, the electrical reactions rose coincidently with the removal of the spasm.

Dog	Normal K.O.C.	Tetany K.O.C.	Abolition of tetany by parathormone	
			Immediately (5-24 hrs.) K.O.C.	2-4 days K.O.C.
1	—	0·35 ma.	0·49 ma.	2·4 ma.
5	5·0	0·42	1·60	—
6	5·0	0·40	3·0	5·0
8	3·0	0·20	1·4	3·0
9	3·5	0·15	1·6	3·0
9	3·5	0·53	1·6	1·35

In tetany abolished by curare, there was no rise in electrical reactions unless the muscles were paralysed by a very large dose of the drug.

Dog	Normal K.O.C.	Tetany K.O.C.	Curare mg.	Abolition of tetany K.O.C.	Paralysis
9	4·0 ma.	0·15 ma.	40·5 ma.	0·40 ma.	Yes
12	5·0	0·50	54·0	1·70	,,
5	5·0	0·42	21·6	0·28	No
6	5·0	0·40	27·0	0·20	Slight weakness

Similarly with a normal dog, we found a rise in the electrical thresholds only when the muscles were paralysed by curare.

Dog	Normal K.O.C.	Curare mg.	Under curare K.O.C.	Paralysis
17	2·9 ma.	48·6 ma.	4·1 ma.	Severe
15	4·5	48·6	5·5	,,
15	3·3	43·2	7·0	,,
11	6·0	32·4	5·0	Slight
11	6·0	40·5	8·0	,,
10	2·1	27·0	3·1	,,

In contradistinction to the above, high dosage with parathormone raises the electrical thresholds of the normal dog, sometimes to figures many times the normal. In one dog in which the normal K.O.C. was 1·2 ma. repeated increasing doses of parathormone raised this to 10·0 ma. This animal had 240 units of parathormone in 120 hours.

We found no rise in the serum calcium on giving curare either in doses adequate to remove tetany or in quantities producing profound paralysis.

A.—*Paralysis of normal dog.*

Dog	Normal	Curare paralysis
15	10·35 mg. per cent.	8·8 mg. per cent.
17	10·9 ,, ,,	10·8 ,, ,,

B.—*Relief of tetany.*

Dog	Normal	Tetany	Abolition of tetany by curare
9	10·5 mg. per cent.	6·8 mg. per cent.	6·7 mg. per cent.
10	11·2 ,, ,,	6·6 ,, ,,	5·0 ,, ,,

Theoretical Considerations.

There are a number of possible explanations of the phenomenon of the abolition of tetany by a dose of curare which does not paralyse the muscles affected, even temporarily.

(1) The action of the curare may represent a degree of myoneural paralysis only. The suddenness and completeness of the relief, combined with the margin between the antitetany and the paralytic dose of the drug, appears to us to render this explanation inacceptable.

(2) In the contractions of muscles produced by tetany, there may be a mechanism of selection of certain fibres. Curare may produce its effect by selective inhibition of the contraction of these same fibres.

In this connection must be mentioned the conclusion of Bremer and his co-workers, that curare acts selectively upon muscle fibres concerned with tone [7]. The abolition of clonic as well as of tonic convulsions suggests a selectivity of a wider nature.

(3) Curare may inhibit some link in an excitation reflex concerned in the production of tetany.

(4) Curare may have a central action upon some factor in the central nervous system which determines the distribution of the tetany contraction.

(5) The drug may act by a direct neutralization of a circulating toxin, the existence of which has repeatedly been postulated in parathyroid tetany.

Summary.

(1) Curare abolishes active parathyroid tetany in dogs, constantly, rapidly and completely, but for a short time only.

(2) Much smaller doses of the drug are required to abolish tetany than those required to cause obvious paresis in either a normal dog or one in active or latent tetany.

(3) The action of curare, in small doses, or in any but those required to produce profound paralysis, is not accompanied by the rise of threshold to electrical stimulation, or by the rise in serum calcium which are constant accompaniments of tetany relieved by calcium or by parathyroid extract.

(4) Certain possible explanations of this action of curare in tetany are considered.

For the serum calcium estimations we are indebted to Dr. E. N. Allott. One of us (R. W.) was in receipt of a grant from the Royal Society, in aid of the above research.

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ON POSTURE AND POSTURAL REFLEX ACTION: THE EFFECT OF UNILATERAL LUMBAR SYMPATHETIC CHAIN EXTIRPATION.

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THIS monograph is an account of a series of observations made on the posture and postural reflex actions of decerebrate cats following removal of the ganglionated sympathetic chain in the lumbar region. The extensor muscles of the knee-joints (vasto-crurei) were selected as the postural muscles to be studied, and the changes in posture and postural reflex activity were examined in fifteen subjects.

These fifteen animals were divided into two groups. In the first group, consisting of eight cats, the left lumbar sympathetic chain was removed, the animals allowed to recover from the operation and then left undisturbed in cages for at least three weeks before decerebration was performed. In the second group, numbering seven cats, the left lumbar sympathetic chain was removed immediately after decerebration was performed.

The lumbar sympathetic chain was in each case extirpated from the level of the last thoracic ganglion to the brim of the pelvis through a mid-line incision in the anterior abdominal wall.

After decerebration, both vasto-crurei muscles in each cat were liberated from extraneous reflex effects by section of all the cutaneous nerves to both hind limbs, and tenotomy or motor-nerve section of all the other muscles in both hind limbs, thus leaving intact only the two vasto-crurei muscles and the branch of the femoral nerve supplying each of them. Each animal was then fixed on the operating table in the following manner. Holes were first drilled through the lower end of each femur and a rigid silver steel rod passed transversely through both holes. The cat was then placed supine on the table and the ends of the steel rod were clamped in two heavy upright cast-iron stands. The height of the steel rod was adjusted so that the caudal end of the cat's trunk was suspended and free from contact with the table. In order to guard against asymmetrical body stimuli, the shoulders were allowed to rest in a V-shaped wooden trough. The head was strapped in the mid-line with the neck in the fully-flexed position.

From the moment of mid-brain section at the operation of decerebration until the conclusion of all observations on each animal, artificial respiration was maintained by a stream of air which was blown into the cat's lungs at a rate varying between sixteen and twenty times a minute, expiration being carried out in the intervals by passive collapse of the chest wall.

Anatomical controls were procured by photographing the extirpated sympathetic chains and the brain-stems removed from each animal at the conclusion of the observations. The integrity of the right lumbar sympathetic chain was investigated in each case by post-mortem examination.

Observations.

(1) *On posture.*—As the decerebrate cat recovered from the anæsthetic the limbs extended and the characteristic attitude of decerebrate rigidity developed.

All four limbs extended in both groups of cats, and if the animal were placed in the normal standing attitude it would remain standing and display no tendency to fall to one side or the other. On attempting to make the animal support the weight of the caudal end of the trunk on one hind leg alone, it became obvious that whereas the right leg would support the hindquarters in the normal posture and at approximately the normal height from the table level, the left leg (the left lumbar sympathetic chain having been removed) would not do this, and under the weight of the hindquarters gradually became flexed until the cat's trunk came to rest on the surface of the table. This phenomenon was constantly observed in both groups of decerebrate animals. With the cat fixed on the table in the manner described, the extensor rigidity was equally persistent in both hind limbs, lasting, in every case, for at least three hours. Flexion of the head caused increased extension of the hind limbs; extension of the head caused a decrease in the extension of the hind limbs; rotation of the head to one side or the other produced a reflex increase in the extension of the limb on the side to which the chin was rotated.

(2) *On postural reflex action.*

(*a*) *Lengthening and shortening reactions.*—On grasping the hind leg of an animal manifesting decerebrate rigidity and attempting to flex it, a considerable resistance is encountered. As the flexing force is increased the resistance suddenly disappears, and the knee-joint is carried easily and rapidly into a flexed position. If the leg be now

released it will not return to its original extended position, but will remain approximately in the position to which it has been carried by the flexing force. The extensor muscle of the knee-joint has therefore taken up a new lengthened posture.

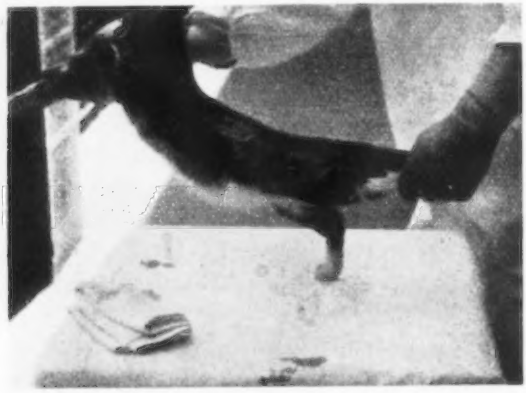

FIG. 1.—Cat No. 2. Caudal end of trunk is supported on the right hind leg. Decerebration and left lumbar sympathetic trunk extirpation performed one hour previously.

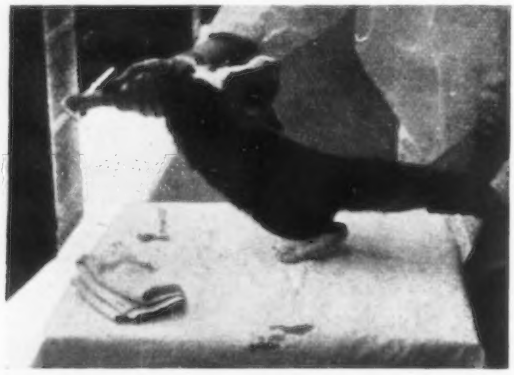

FIG. 2.—Cat No. 2. Caudal end of trunk cannot be supported by the left hind leg. Decerebration and left lumbar sympathetic trunk extirpation performed one hour previously.

Sherrington [1] has shown that this lengthening reaction is a reflex action subserved by a nervous arc, the afferent endings of which are proprioceptive in nature and are situated in the substance of the extensor muscle itself. The adequate stimulus for the excitation of the nerve endings is stretching of the muscle fibres among which they lie.

To elicit the shortening reaction the flexed knee-joint is passively extended, and on releasing the leg it is seen to remain in approximately the extended position to which it has been moved. Here the extensor muscle of the knee-joint has taken up a new shortened posture. This shortening reaction is a reflex action subserved by a nervous mechanism similar to that which mediates the lengthening reaction. In both groups of decerebrate cats lengthening and shortening reactions were constantly present in the vasto-crurei muscles of both sides. They could always be elicited by passive manipulation of the hind limbs.

On grasping the lower ends of the tibia simultaneously, one in each hand, with the animal in the fixed position on the table, and applying a gradually increasing flexing force, the characteristic resistance offered by the contraction of the vasto-crureus produced by the myotatic or stretch reflex was at first encountered in both limbs.

As the flexing force on each side was gradually and equally increased, the resistance offered by the left vasto-crureus was felt to yield under a flexing force which continued to produce a strong myotatic contraction on the right side; this flexing force thus produced a lengthening reaction on the left side and the left knee-joint was carried into a flexed position. As the flexing force was further increased on the right side, the myotatic contraction of the right vasto-crureus was finally overcome, the lengthening reaction was elicited and the right knee-joint carried into a flexed position.

This phenomenon was observed in every cat examined. When a load of 500 grams was suspended from the lower end of each tibia of a decerebrate cat in the fixed supine position, the left lumbar sympathetic trunk having been removed, the weight on the left side appeared to sink down gradually at an even rate until it came to rest upon the table; the weight on the right side, however, sank more gradually at first and, slowing down, came practically to rest some distance above the table, and finally sank slowly through the remaining distance to come to rest on the table.

The weight on the left side always appeared to reach the table from three to five seconds before that on the right side.

(*b*) *Crossed extensor reflexes.*—The crossed extensor reflex was first described by Philippson [2], and later more fully detailed by Sherrington. It consists in the reflex contraction of the lengthened vasto-crureus muscle of one side by the forceful passive extension of the opposite shortened tonic vasto-crureus. With the decerebrate cat in the fixed supine position manifesting rigidity in both hind limbs, the lengthening

reaction was elicited in the left vasto-crureus by forceful passive flexion of the left knee-joint.

The posture now presented was extension of the right leg and flexion of the left. This asymmetrical posture of the hind limbs is the appro-

FIG. 3.—Cat No. 117. Decerebration two hours previously. Left lumbar sympathetic trunk removed twenty-one days previously. Posture of left hind leg after passive flexion of left knee-joint.

FIG. 4.—Increased extension of left knee-joint and alteration of posture produced by tapping the patellar tendon *once* with a percussion hammer.

priate attitude for the examination of the crossed extensor reflexes. If the right leg be grasped and the tonic right vasto-crureus forcibly extended, a reflex contraction is produced in the left vasto-crureus and the left knee-joint takes up an extended posture.

This reflex contraction may now be produced on the right side by forceful passive extension of the tonic left vasto-crureus. These reflexes are subserved by nervous arcs, the afferent nerve endings of which are proprioceptive in nature and are situated in the substance of the vasto-crurei muscles. In both groups of decerebrate cats these reflexes were present in every case in both hind limbs. They were recorded myographically by attaching the lower ends of the animal's tibiæ to isotonic levers. It was observed, after removal of the left lumbar sympathetic chain, that the strength and amplitude of the motor response of the crossed extensor reflex was greater on the right side than on the left when an equal or a maximal amplitude of forcible passive extension was

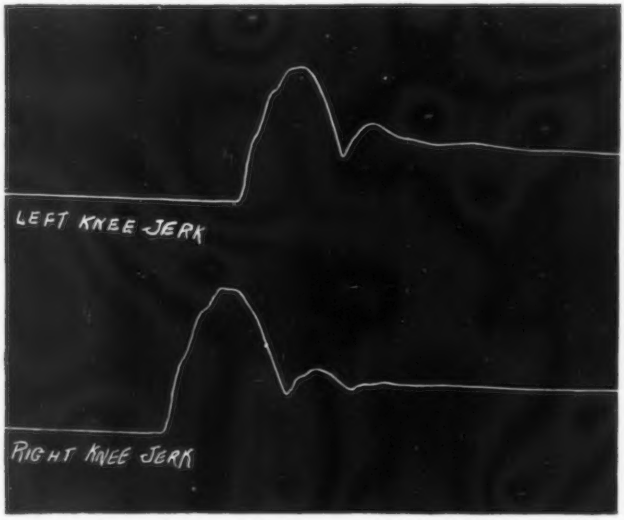

FIG. 5.—Records of knee-jerks of decerebrate cat, No. 10; decerebration performed three hours previously. Left lumbar sympathetic trunk removed at the same operation.

applied to the appropriate tonic muscle. It was also observed that the amplitude of passive extension required to produce a minimal motor response in the opposite muscle was always less on the left side.

(*c*) *Knee-jerks.*—The knee-jerks were examined by inspection and myographic records made of them in both groups of decerebate cats. The jerks were elicited by tapping the patellar tendon with a small percussion hammer. If after passively flexing the knee-joint the patellar tendon were tapped several times with the percussion hammer, the joint presented a more extended posture after each tap until the original extended posture was finally regained (see figs. 3 and 4).

In recording the knee-jerks a lever system was used that was designed particularly to demonstrate the presence or absence of the myotatic or stretch reflex following the phasic response. This instrument consisted briefly of an isotonic lever, checked by a spring which prevented overthrow and maintained a slight persistent stretch on the postural muscle. A myogram of the knee-jerks is reproduced in fig. 5. In both groups of decerebrate cats the records of the knee-jerks showed that after the upward fling of the phasic response of the knee-jerk the extensor muscle on the left side (the left lumbar sympathetic chain having been removed) did not relax as far as the corresponding muscle on the opposite side, and that the left vasto-crureus came to rest at a shorter length than the right vasto-crureus, an observation that was made clear by the fact that the level of the tracing on the left side was higher following the knee-jerk than it was on the right side.

Discussion.

It may be concluded from the preceding experiments that decerebrate rigidity develops and is maintained in the left hind limbs of decerebrate cats after removal of the left lumbar sympathetic chain. The postural reflexes exhibited by isolated postural muscle preparations are qualitatively unaltered by removal of the appropriate sympathetic nerve chain.

It must be concluded therefore that the post-ganglionic fibres of the sympathetic nervous system do not constitute the efferent limb of the reflex nervous arc subserving posture in skeletal muscle.

The positive changes in posture and postural reflex actions following removal of the left lumbar sympathetic chain in decerebrate cats may be summarized as follows:—

(1) The caudal end of the trunk can be supported at the normal standing height by the right leg but not by the left.

(2) A passive flexing force which on the left side is sufficiently great to elicit the lengthening reaction produces on the right side a myotatic contraction due to the stretch reflex. Further increase of this force on the right side elicits the lengthening reaction.

(3) The amplitude of the motor response of the crossed extensor reflex (Philippson's) is greater on the right side than on the left.

(4) The crossed extensor reflex may be produced on the right side by a smaller stimulus (less stretch) than is required for its production on the left side.

(5) The knee-jerk is followed by a myotatic contraction which on

the left side appears earlier during relaxation and is therefore produced by a smaller stimulus (less stretch) than the normal myotatic response on the right side.

Consider first the changes observed in the crossed extensor reflex. It has been noted that a smaller stimulus (less stretch) is required on the left side to produce a crossed reflex than is necessary on the right side. Left lumbar sympathetic chain removal could produce this effect in two ways.

(1) By increasing the excitability of the receptor nerve endings in the left vasto-crureus muscle; (2) by depressing the activity of the effector nerve endings in the left vasto-crureus muscle.

Consider these two possibilities in the light of the changes produced in the left knee-jerk by the same operative procedure. In this case after left lumbar sympathetic chain removal the left knee-jerk is followed by a postural (myotatic) contraction which appears earlier during relaxation than it does on the opposite normal side. Removal of the left lumbar sympathetic chain could also produce this change in two ways:—

(1) By increasing the excitability of the receptor nerve endings in the left vasto-crureus muscle; (2) by increasing the activity of the effector nerve endings in the same muscle.

From the consideration of these two postural reflex actions therefore, it seems probable that removal of the left lumbar sympathetic chain has increased the excitability of the proprioceptive nerve endings situated in the left vasto-crureus muscle.

When the lower end of the tibia of a decerebrate cat manifesting decerebrate rigidity is grasped and a gradually increasing flexing force is applied, the stretching of the postural muscles elicits in them a myotatic contraction through a proprioceptive reflex arc and a resistance is offered to the flexing force. As the force is increased, however, and the postural muscles are still further stretched, another type of proprioceptive nerve ending is stimulated at a certain threshold of tension in the muscle fibres. This new type of nerve ending inhibits the myotatic contract on and the leg may now be carried into a fully flexed position without any further increase in the flexing force. This lengthening reaction can be seen therefore to form, as it were, a background to the myotatic contraction. It only becomes obvious when the tension in the muscle fibres rises above a certain threshold value.

It can be seen therefore that if removal of the left lumbar sympathetic chain produces an increased excitability of the receptors in the

left vasto-crureus muscle, not only will the myotatic contraction occur earlier when this muscle is stretched (which was noted to be the case following the knee-jerk), but also the threshold of tension necessary to elicit the lengthening reaction will be lower. This latter observation was seen to be true when two equal and gradually increasing flexing forces were applied to the hind limbs of a decerebrate cat after removal of the left lumbar sympathetic chain. The threshold of tension necessary to elicit the lengthening reaction was always arrived at more rapidly on the left side, and the left leg carried into flexion by a force which still continued to produce a myotatic contraction on the right side.

All the changes in posture and postural reflex activity that were observed to follow removal of the left lumbar sympathetic chain may be explained by the hypothesis that the effect of removing the sympathetic innervation to the vasto-crureus muscle was to increase the excitability of the receptor nerve endings situated within its substance. This hypothesis may throw some light on the functional significance of the fine non-medullated nerve fibres which have been noted to pass to muscle spindles and other proprioceptive end organs [3]. The origin of these fibres is still unknown, although Kulchitsky [4] believes that they are derived from the sympathetic nervous system. It is possible, however, that these fibres have some influence over the blood-supply or metabolism of the muscle spindles, and it is conceivable that their removal might readily disturb the excitability of those proprioceptive nerve endings subserving posture in skeletal muscle.

Whatever may be the explanation for the changes in posture and postural reflex activity in skeletal muscle following removal of its sympathetic innervation, nevertheless the author wishes to reiterate that skeletal muscle still exhibits postural tonus after removal of its sympathetic innervation. Postural contraction is not abolished by this procedure and reflex postural activity seems to be enhanced. All changes in postural tonus following sympathetic extirpation appear to be quantitative rather than qualitative in nature.

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TWO CASES OF OLIGODENDROGLIOMA:

With Remarks on the General Clinical Features of such Cases.

BY J. PURDON MARTIN.

Introduction.

The tumours that have been called oligodendrogliomas form one of the better demarcated groups among the tumours that arise from cerebral tissues. Their histological picture is quite unlike that of any other cerebral growth. In their clinical features no absolute peculiarity has yet been recognized, but there is a certain constancy, and my primary object in this paper has been to review the clinical characters of my own cases and those previously recorded and see whether the clinical picture could not be made more precise. At the same time such deductions with regard to the life history of oligodendrogliomas as seemed legitimate from the clinical histories have been pointed out. In the account of my second case a larger pathological element has been introduced, because it seemed imperative to give a description of the very unusual features found after the patient's death.

In the two cases described in this paper the masses of tumour removed from the brain at operation were found on histological examination to consist almost entirely of small cells, of which the nuclei were easily stained, but the cytoplasm was indefinite and almost unstainable by any of the ordinary methods (figs. 2 and 6). Tumours showing this peculiar structure had been described by various writers before the recognition of oligodendroglia, and their origin had been attributed in one or two cases to the "third element" of Cajal. Bailey and Cushing [3] first suggested that these peculiar tumours arose from that fraction of the third element which had been named oligodendroglia, and they applied to them more or less tentatively the name "oligodendroglioma." In 1929 the subject was advanced further by the publication of an important paper by Bailey and Bucy [2]. These workers examined tumours of this type by the specific oligodendroglia stains of Hortega and of Penfield, and found that the cytoplasm of their cells stained deeply by these methods, and that it possessed elongated

expansions similar to those of oligodendroglia. Some of the cells showed modifications in their form and in their staining reactions, which seemed to indicate that they were in stages of development or of degeneration, and there were many cells which seemed to be intermediate forms between oligodendroglia cells and astrocytes, but the conclusion was that these tumours were composed essentially of oligodendroglia.

The pathology of oligodendrogliomas has been fully dealt with by Bailey and Bucy, and no general discussion of it need be given here. For their recognition, recourse to the intricate specific staining methods for oligodendroglia is not necessary, because the histological picture obtained with ordinary stains is quite distinctive. In the accounts of the individual cases which follow instances of this picture will be described.

Oligodendrogliomas are rare tumours. Those described in this paper are the only ones that have been encountered at the National Hospital during the last ten years, and there is only one case recorded in the recent literature in this country. These facts, however, probably give an exaggerated idea of their rarity. Bailey and Cushing [3] found nine oligodendrogliomas among the 300 gliomatous tumours on which their monograph was based; Bailey and Bucy later described four others from the same clinic. Roussy, Lhermitte and Cornil [8] included a case in their study of the gliomas, and Schaffer [9] has also described one. Clinical accounts are given in four only of the cases recorded prior to Bailey and Bucy's paper [2]. Bailey and Bucy, including in their paper the cases previously referred to by Bailey and Cushing, gave full clinical records of four cases, and showed in a table some of the clinical features of nine other cases.

Case 1.—In September, 1929, Sir Percy Sargent operated on a patient of mine at the National Hospital, Queen Square, and removed from the left frontal lobe a mass of tumour which, on microscopical examination, was found to be an oligodendroglioma.

The patient, A. H., was a male, aged 38 at the time of operation. He had been employed as a railway worker for twenty-two years, and for five years had been an engine-driver, and was graded as a "First-class driver."

In the summer of 1925 he began to have occasional pain in the left half of the forehead, and on December 18, of the same year, he had a fit while asleep. After that he remained well except for occasional headaches until June, 1927, when he had a second fit. He then consulted a doctor and was put under treatment for epilepsy. During the next fifteen months he had no fits, but still had occasional frontal headaches, and "one or two turns of vomiting."

After the third convulsion, I examined him at the National Hospital, on October 3, 1928. The patient was quite normal mentally, and power, sensation and the reflexes were unaltered in all parts of the body. He was admitted to the hospital on November 26, 1928, and remained until December 19. Repeated clinical examination revealed no abnormality; the optic discs, though at first suspiciously red, were within the limits of the normal: the cerebrospinal fluid was normal and its pressure was not definitely raised (145 mm. of fluid).

In the X-ray films of the skull no abnormality was detected at that time, but the films, because of difficulty with the X-ray tubes, were not very good. On December 1 the patient had a group of three fits; these were generalized convulsions of sudden onset: the head and eyes turned forcibly to the right but otherwise the attacks presented no localizing features; no weakness or aphasia was observed after these attacks. In the next few days six more attacks occurred, all similar to those of the first group though less severe. At the end of June, 1929, I saw the patient again; he had not suffered even from a headache since his discharge from hospital and declared that he had never felt better in his life. He had been employed continuously since his discharge from hospital as a lamp-cleaner in the railway workshops. He remained free from obvious symptoms until the end of August, 1929. Then he had a severe bout of fits, followed by prolonged unconsciousness (lasting more than forty-eight hours) and was admitted in an unconscious state to the hospital at Peterborough. He was transferred to the National Hospital on September 6, 1929. Examination then showed bilateral choked disc but the functions of the cranial nerves were otherwise unaffected: power and sensation were normal in the limbs and there was no dysdiadochokinesis, but a fine tremor was present in the left hand; the abdominal reflexes were present but weaker on the right side than on the left; the tendon-jerks were equal on the two sides and the plantar reflexes were flexor as a rule, but the right was somewhat indefinite. He was taciturn and looked sullen, but he accepted all decisions without a murmur: he showed no defect in intelligence. The cerebrospinal fluid was normal, but its pressure was over 300 mm. of fluid and fell very little after the withdrawal of 5 c.c. of the fluid. Stereoscopic X-ray films showed an irregular stippled opacity in the left frontal region (Plate VIII, fig. 1); it lay close to the middle line and apparently towards the upper surface of the frontal lobe, spreading out in a position corresponding to the medial half of the superior surface of the lobe; the shadow did not appear to extend to the tip of the lobe either on the medial or superior surfaces. No change was seen in the bones of the skull. Re-examination of the films taken in November, 1928, now showed a blurred shadow of calcareous deposits in the same situation.

At the operation when the superior surface of the left frontal lobe was exposed, the tumour was seen at the anterior and upper corner of the bony opening. It was not attached to the dura. At first it seemed to be attached to the arachnoid, for when this was snipped through an edge of tumour could be raised from the surface of the brain. It was a dark bluish-red mass,

slightly lobulated, and seemed at first to be overlying the brain. When its middle portion had been shrivelled by diathermy the peripheral part was gently raised from the brain and it was then found that the tumour extended deeply into the substance of the frontal lobe. A mass about the size of a small tangerine orange was removed, but the most anterior part of the tumour was not reached. Very little hæmorrhage resulted from the removal.

On the day following the operation the patient had a partial right hemiplegia and was completely aphasic, but he soon improved, and by the end of three weeks he was apparently completely well. He was given an intensive course of radium treatment and finally left hospital on December 4, 1929. At the time of his discharge the scalp flap in the operation area was not tense; the swelling of the optic discs had subsided without impairment of the visual acuity, and the functions of the other cranial nerves were normal; in the limbs the only abnormality was a fine tremor of the hands, definitely more pronounced in the left; there was no aphasia or apraxia; reading, writing and arithmetic were well performed and his memory was good; the only defect noticed in his mental functions was inability to describe spontaneously a sequence of events with which he was quite familiar, e.g., the path of the steam in the mechanism of a railway engine, though questioning showed that he understood the sequence. A small calcium-stippled mass was still shown in the brain by X-rays.

After histological examination of the mass removed at the operation, Dr. Greenfield reported: The specimen consists of several fairly large masses of tumour of a pinkish-red colour, which appear, to the naked eye, to be composed of a thick, fleshy outer part with a degenerated centre. *Histologically* the tumour is composed of masses of cells with small rounded nuclei and very indefinite cytoplasm. An indefinite matrix appears at the outer margin of the cytoplasm, but there is a circular zone of unstained or indefinitely granular material round the nucleus, which is limited by a faintly outlined cell capsule (Plate VIII, fig. 2, and Plate IX, fig. 3).

Blood-vessels of not much more than capillary diameter, but with thickish endothelial walls, are very numerous and rather regularly arranged, separating trabeculæ of tumour cells of about equal width. In the degenerated areas there are fairly thick bands of collagen representing the lines of the vessels but no nuclei are stained in these or in the intervening tissue. Between the degenerated portions and the more healthy tumour tissue are areas containing numerous, irregularly shaped, calcified knots, lying in a tissue which resembles dense neuroglia with fairly abundant trabeculæ.

The histological structure of the main mass of the tumour resembles closely oligodendroglia, and the tumour agrees well with the description of *oligodendroglioma*.

Progress after discharge.—The patient was seen in the out-patient department at intervals up till July, 1930, and was kept on luminal and bromide as a precautionary measure. At his first attendance he reported that he had had a fit; this was a mild, generalized convulsion which had begun with turning of

the head and eyes to the right; after a few minutes he was quite well again. The scalp flap remained soft and the patient had no headaches. Intellectually and emotionally he seemed normal, and with the exception of a fine tremor of the left hand he presented no abnormal physical signs. He was still in this condition when he last attended (July 15, 1930), and for many months he had been working as an engine-driver in a restricted capacity. No further news of him was received until after his death. It appears that about the middle of October he began to show symptoms again. He became "dazed," and as he was making mistakes at his work he was discharged. His manner changed and he became indifferent. He then developed ptosis of his left eye and spasticity of his right leg, with an exaggerated knee-jerk, ankle clonus and a positive Babinski reflex. Later he became incontinent of urine and fæces and gradually became unconscious. He died on November 9, 1930. Throughout this last phase there were no local signs at the seat of operation.

The period of survival after operation was thirteen and a half months.

Comment on Case 1.—This case may be taken as a characteristic instance of oligodendroglioma. Typical features are: the age of the patient (35 to 38), the long history of symptoms, the absence of paralytic and the presence of "irritative" symptoms, the long remissions of symptoms, the presence in the tumour of calcareous deposits visible on the X-ray films and the fact that the tumour was situated in the frontal lobe. The primary result of the operation was excellent. The histological picture was characteristic, even to the presence of endothelial proliferation in the small blood-vessels. The scarcity of mitotic figures indicated the slowly growing nature of the tumour.

Case 2.—Two months after this first patient had been discharged from hospital, another case, which eventually proved to be one of oligodendroglioma, was admitted under the care of Dr. Hinds Howell.

E. C., male aged 43, a labourer. He complained of severe headaches of five weeks duration and of some unsteadiness in walking which had been present since an accident nine weeks previously. The patient showed a good deal of mental confusion. The history, obtained partly from the patient and partly from his daughter, was as follows: He had been healthy until three years before. Then he was knocked off his bicycle by a car and was unconscious for several minutes. There was, however, no indication of serious injury. After this he often complained of pain in the head, and there were periods in which he contradicted himself frequently in speech without realizing that he had done so. His headaches and confusion did not interfere with his work as a stoker. About a year before his admission he had complained very greatly of pain in his head and of "a film coming over his eyes." Nine weeks before admission he had a second accident; a bus in which he was travelling home from work collided with another vehicle and the patient was thrown against the seats and

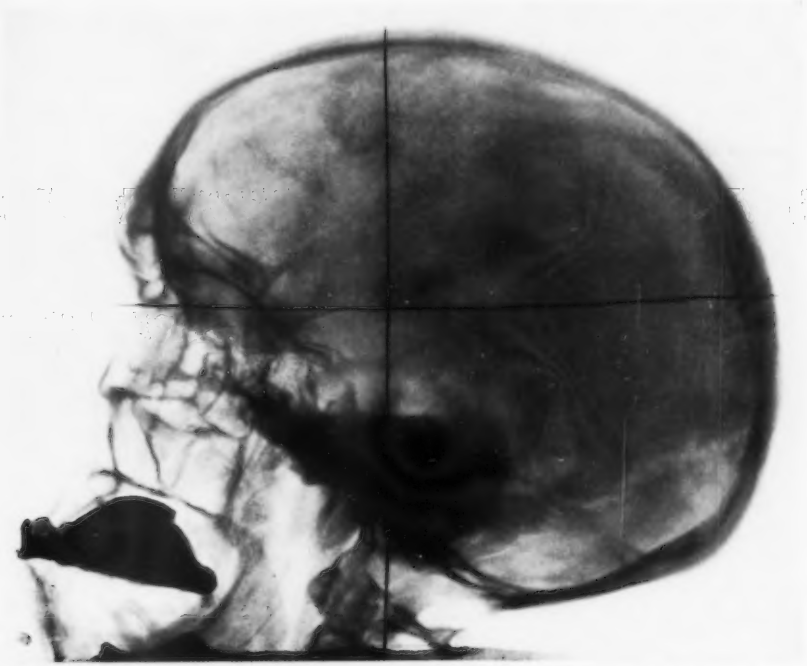


FIG. 1 (*Case* 1).—X-ray photograph of the patient's head, showing calcified deposits in the left frontal area.

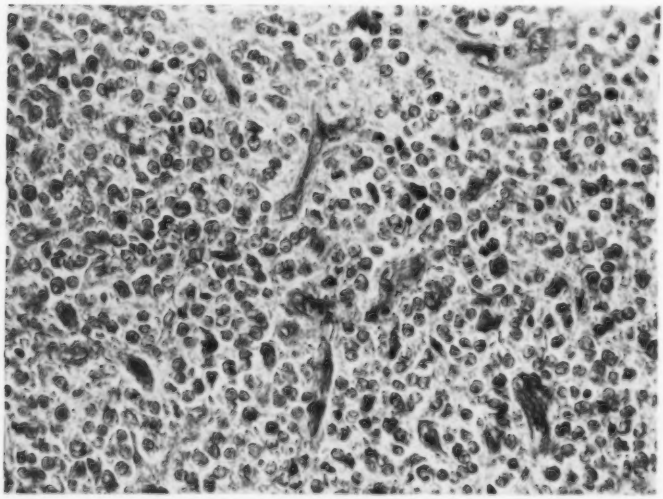


FIG. 2 (*Case* 1).—A section of the tumour. × 300. Hæmatoxylin and van Gieson. See the description in the text.

To illustrate paper by J. Purdon Martin.

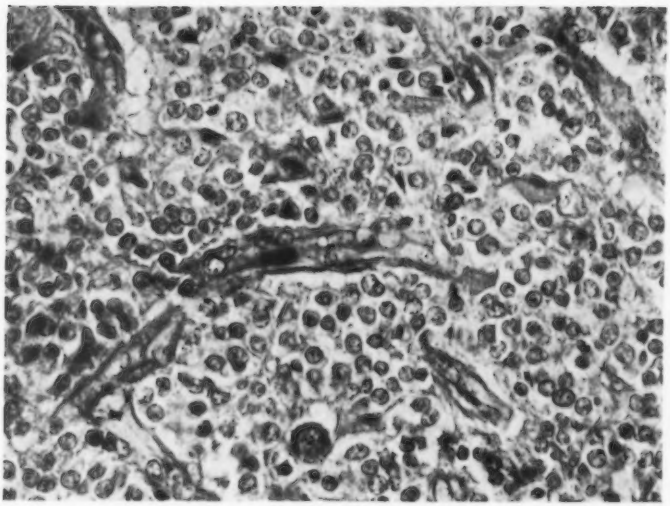


FIG. 3 (*Case* 1).—Another portion of the tumour. × 400. Same staining as in fig. 2. Nerve cells are present, though undergoing degeneration.

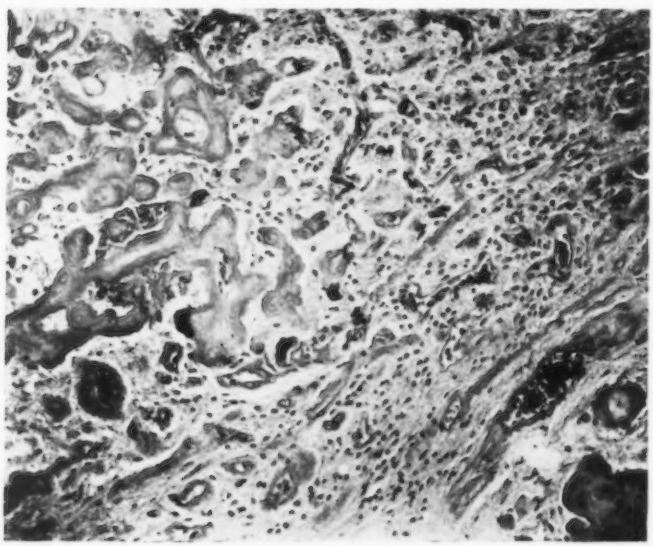


FIG. 4 (*Case* 1).—Another portion of the tumour after (incomplete) decalcification. The calcium deposits are primarily in the walls of blood-vessels.

To illustrate paper by J. Purdon Martin.

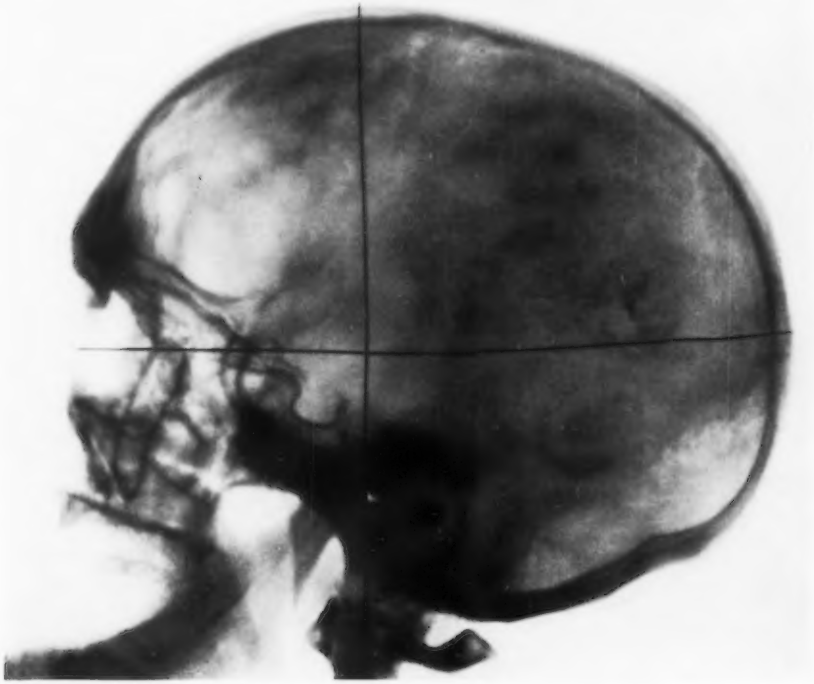


FIG. 5 (*Case* 2).—X-ray photograph of the patient's head, showing extensive calcification in the left parietal region.

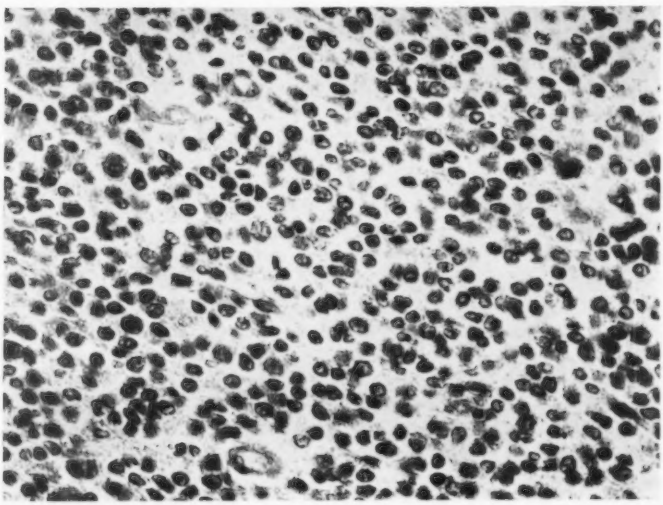


FIG. 6 (*Case* 2).—A section of the tumour. × 400. Hæmatoxylin and van Gieson. See the description in the text.

To illustrate paper by J. Purdon Martin.

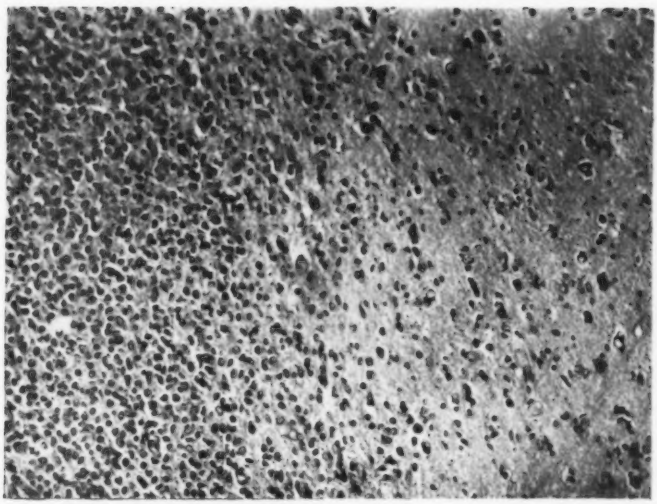


FIG. 7 (*Case* 2).—The edge of the tumour. × 150 (15 cm. represent 1 mm.). The transition from apparently healthy brain to tumour takes place over a space of about half a millimetre. From left to right in the figure the satellites of the nerve cells become rapidly more numerous. Same staining as fig. 6.

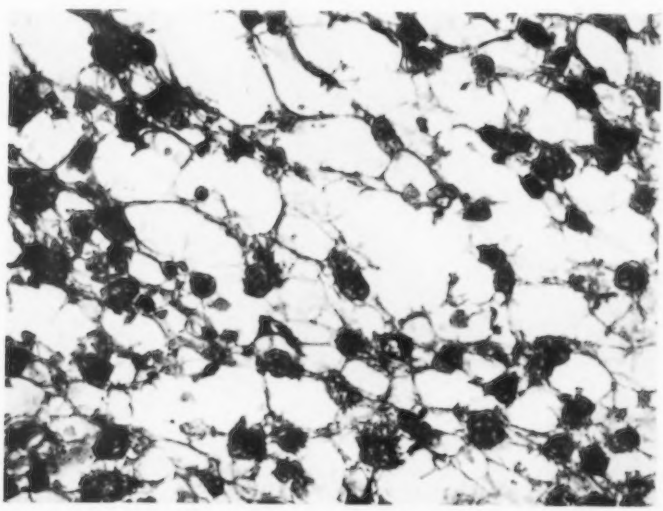


FIG. 8 (*Case* 2).—High-power view of a section of the tumour from the fourth ventricle. Mallory's stain. Note the apparent branching of the cells and the resulting network.

To illustrate paper by J. Purdon Martin.

his legs and back were bruised. He seems to have been definitely worse after this accident. He suffered from severe headaches, his sight became gradually worse, and he was unable to work. His right hand became unsteady and, in consequence, he was unable to write. He also had some unsteadiness in walking, and on several occasions he fell in the street. His memory became bad and he was mentally confused. He had never had any kind of fit and there had been no vomiting associated with his headaches.

Condition on admission.—The patient's intelligence was well below the average. Cerebration was slow. He was easily confused and his memory was poor. He presented no defect of speech and he made no mistakes in writing. Papillœdema was present in both eyes, the swelling amounting to about three dioptres in each. The visual acuity was, however, normal, and the visual fields were full. Some weakness was observed at the right angle of the mouth and the right eye could be opened against the patient's resistance rather more easily than the left. Otherwise the functions of the cranial nerves were normal. On the left half of the body no abnormal signs were detected. On the right side there was a slight tremor of the hand. Appreciation of passive movements of the fingers was not so good as on the left side, and discrimination of compass points was definitely worse on the right hand and forearm than on the left, but sensation was otherwise normal. The right abdominal reflexes were usually absent, and if present, tired easily. No weakness or inco-ordination of movement was found. The tendon-jerks were normal and the plantar reflexes flexor. The patient was more unsteady when standing on the right foot than when on the left, but his gait and usual stance were normal.

The alimentary, respiratory, and urinary systems were normal. The pressure of the cerebrospinal fluid was well over 300 mm. of fluid, and after the withdrawal of 5 c.c. of fluid it was still 280 mm. The fluid was slightly yellow, the total protein content amounted to 0·20 per cent. and the globulin tests were fairly strongly positive. The Lange curve did not rise above 2 in any tube. There were five cells per c.mm., all mononuclear. The Wassermann reaction was negative both in the cerebrospinal fluid and blood.

Stereoscopic X-rays of the skull showed little flecks and irregular streaks of calcification throughout a globular space in the left parietal region (Plate X, fig. 5).

The patient was operated on by Sir Percy Sargent on February 28, 1930. A large parietal bone flap having been turned down, some discoloration could be seen through the dura, and when the brain was exposed, a dark bluish-red tumour was found lying in the parietal lobe behind the post-central gyrus; the area of visible tumour was about the size of a two-shilling piece. With the aid of diathermy the tumour was demarcated and its more superficial parts separated from the brain substance; pieces forming altogether a mass as big as a hen's egg were then removed. There seemed to be a pedicle passing into the substance of the brain towards the corpus callosum. The tumour substance felt gritty. Radium needles were implanted in the tumour and the flap and wound were closed.

The patient made an excellent recovery and was discharged six weeks later.

The right arm when extended showed slight unsteadiness, but co-ordination in ordinary movements was good. There was no weakness of the limbs and the gait was good. Visual functions and speech were undisturbed.

Pathologist's report (Dr. Greenfield).—This is a very cellular tumour, composed of rounded or oval nuclei with very little cytoplasm between them (Plate X, fig. 6). What matrix is visible is indefinitely fibrillar and does not begin immediately round the nucleus, but in most places leaves a clear unstained circle round it. In some parts, there is, however, a more abundant matrix of a similar, ill-defined, fibrillar structure. Mitotic figures are very numerous. In some portions of the growth there is a considerable infiltration with connective tissue fibrils even between the tumour cells, and fine capillaries are abundant. The tumour has a fairly well defined margin in some places (Plate XI, fig. 7), but in others there is a transition from tumour to normal brain tissue through a wider zone of excessive cellularity. In one place numerous small gritty knots of calcification are present in the tumour.

The characteristics of the tumour approximate closely to those of the tumours described as *oligodendrogliomas*.

Progress after discharge.—This patient after his discharge from hospital remained relatively well for several months, but he suffered from headaches and was somewhat dull mentally, and consequently did not return to his work. After nine months he was re-admitted to the hospital. Ataxia of his right leg and astereognosis in his right hand were then definite and his speech was confused; his cerebration was slow, he was drowsy and suffered much from headaches. There was a large cerebral hernia. Further operation was inadvisable and the patient died on February 9, 1930, eleven and a half months after his operation.

A post-mortem examination was performed by Dr. Greenfield fifteen hours after death.

When the scalp was being dissected anterior to the margin of the cerebral hernia, a small nodule, which appeared to be new growth, was found above and in front of the left ear. It was irregularly spherical and measured 1 cm. in diameter.

When the calvarium was removed the dura was found adherent in many places over the posterior half of the left cerebral hemisphere, but there was no invasion of it by new growth. Under it the tumour was visible occupying the medial half of the superior surface and the whole of the medial surface of the left parietal lobe. The outward appearance of the tumour, though mottled, was in most parts greyish and granular. Sections through the brain after fixation showed that the tumour was very large, occupying most of the parietal lobe and of the occipital lobe above the calcarine fissure. Medially, it invaded the splenium of the corpus callosum. It had invaded and largely filled the body and posterior horn of the left lateral ventricle. Below, the main mass of the growth involved the roof of the inferior horn in its posterior part. In the floor of this horn, right to its tip, there was an elongated extension from the tumour mass in the body of the ventricle. This extension was 3 or 4 mm. wide. It

was pale, glistening and gelatinous-looking, just a little greyer (after fixation) than the white matter of the hemisphere. Along the floor of the anterior horn on this left side there was a thicker, wider and firmer deposit of similar glistening appearance.

In the third ventricle the anterior half was distended with growth of a mottled red colour, which invaded the walls of the infundibular portion and involved the optic chiasma. The posterior half of the third ventricle was thickly incrusted with growth similar in appearance to that in the horns of the left lateral ventricle.

In the right lateral ventricle there was an elongated, pale, glistening deposit along the floor of the anterior horn to its tip. This seemed to have a fine connection through the foramen of Munro with the mass in the third ventricle. On the floor of this right ventricle, at the junction of the posterior and inferior horns, there were two small masses of growth of the same pale gelatinous appearance. These were small circular bosses, each about 3 mm. in diameter. They were separate from each other and from all other growth. No growth was seen in the body of the right lateral ventricle or in its inferior horn. It could not be determined with the naked eye whether there was any extension of the growth from the third ventricle through the aqueduct of Sylvius, but the microscope showed that there were very delicate deposits on the ependyma of the aqueduct, and these were apparently continuous with the mass of growth in the third ventricle. In the fourth ventricle almost the whole of the floor was lightly frosted with growth of the same semi-transparent gelatinous appearance as in the horns of the lateral ventricles.

On microscopical examination the main mass of the growth showed the characters already found in the portion excised at operation. One feature that was more evident was that along small arteries the cells were arranged in rows, and broad prolongations of what was apparently cytoplasm extended down towards the vessel walls.

The pale gelatinous-looking masses in the floor of the ventricular horns and in the fourth ventricle were composed of very loosely formed tissue. (Fig. 8.) In celloidin sections stained with hæmatoxylin and Van Gieson's stain the nuclei, in places widely separated, almost seemed to lie free as in a smear. Faint shadows of unstained fibres could, however, be detected in the spaces between them as one moved the fine adjustment of the microscope and there were some portions of the tumours in which these fibres were lightly stained and could be seen clearly. The nuclei were of the same nature as in the main tumour, but they showed more variation in size and shape. Mitotic figures were very numerous. In paraffin sections stained in the same way the internuclear substance was more evident, but it stained indefinitely and it may be that to some extent the appearances seen in these sections were artefacts. In general, however, the appearances were confirmed by other sections. The cells appeared to possess branches and these branches joined and intertwined and the nuclei appeared as if caught in the net. In some places the nuclei were numerous and the amount of network relatively scant, while in other places, especially

towards the base of each small tumour, the network was denser and the number of nuclei small. The branches in these sections appeared coarser than neuroglia fibres. Both paraffin and celloidin sections showed this network when stained with Mallory's connective tissue stain. In the looser parts of the tumour it took on a faint purplish colour, but where the growth was evidently older and firmer and the fibres formed a denser network their colour approached more closely to that taken by neuroglia fibres. In paraffin sections stained by Perdrau's method the network appeared to be formed by the union of prolongations of a granular cytoplasm which surrounded the nuclei; it did not take the silver stain at all intensely.

Cells departing from the general type were occasionally seen in all the sections and a few were large glial cells. Atypical cells were especially frequent in certain parts of the growth, e.g., in the tumour at the anterior end of the fourth ventricle. There giant cells were relatively numerous and the "transitional" forms illustrated by Bailey and Bucy [2] were to be recognized.

In these small masses of growth blood-vessels were numerous and they often had very thin walls. Along the more fully formed arterioles the tumour cells lay in dense rows, and on the side of each nucleus next the artery a mass of indefinitely stained cytoplasm extended towards the vessel. In the paraffin sections stained by Mallory's method a light purple stained fibre appeared to pass from this cytoplasmic mass on to the adventitia of the artery, and in at least one place these extensions on to the vessel seemed to have expanded feet. When the artery had been cut transversely by the section, the tumour cells were seen ranged in a rosette around it.

Where the incrustations on the ependymal surfaces were thick the brain tissue was invaded and there was an evident neuroglial reaction. But where the deposits were lightest, the ependyma under them was destroyed with little invasion of the sub-ependymal tissue; the growth had evidently been implanted on or skimmed along the ependyma.

The nodule which was found in the scalp showed an irregular mass of cells surrounded by dense fibrous tissue and divided by occasional incomplete fibrous septa. The cells had deeply staining nuclei and no appreciable cytoplasm in the hæmatoxylin and Van Gieson sections. They were massed most densely close to the fibrous septa. The nuclei were smaller and more deeply stained than in most parts of the cerebral growth, but they were very similar to those in the densest part of the latter, and where the staining was not too intense the same granular appearance could be made out in them.

Comment on Case 2.—This case had a more malignant course than the previous one, and than most of those that have been recorded. In the symptoms themselves there was nothing very unusual, but the absence of all "irritative" phenomena may be noticed. In some other ways, e.g., in the age of the patient, the duration of the symptoms, the presence of calcareous deposits in the tumour, and the favourable

primary result of operation in spite of the large size of the tumour, it resembled Case 1. In its pathological aspects it had many unusual features. The tumour showed far more mitotic figures and was evidently of a more actively growing nature than any other oligodendroglioma of which I have seen a description. A more striking feature was the spread of the growth into all the ventricles. In the anterior horns of the lateral ventricles and in the fourth ventricle the deposits may have formed in one of two ways. All the strips of tumour tissue in these situations were continuous with each other and with the main mass, and so may have grown by extension of the main tumour without any breach of continuity. But in the right lateral ventricle, at the junction of its posterior and inferior horns, there were two little bosses of tumour quite separated from any other growth. These must have arisen from "seeds" of tumour carried in the cerebrospinal fluid and deposited on the ependyma—i.e., they are metastases. Several features of the strips and bosses of tumour in the rest of the ventricular system make it likely that they, too, arose largely as metastases from tumour cells carried by the cerebrospinal fluid. They lay along the floors of the horns where deposits from the fluid are likely to fall; their blood-vessels came from the underlying tissue and not from the direction of the main mass; and judging from their fairly uniform thickness the proximal parts were no older than the distal.

The structure of these small masses evidently shows how oligodendroglioma may grow when freed from mechanical pressure. The tissue is very loosely formed and to the naked eye has a glistening or translucent appearance. But the most remarkable feature is the evident branching of the cells and the apparent formation by them of a delicate supporting framework for the growth. Where the cells were packed closely together, as in the main tumour and in certain sections of tumour in the fourth ventricle, no branches could be seen; but where the formation was much more open, e.g., at the anterior end of the fourth ventricle, and, in particular, in the delicate strands of growth in the aqueduct of Sylvius, the network of fibres, and to a less extent the cytoplasm round the nuclei, were visible in all the sections. Where they took up an adequate amount of stain, as in the sections prepared by Mallory's method, the appearance of the cells and branches corresponded closely with those in the pictures of oligodendroglia given in Penfield's paper [7], with the exception that the branches of the cells seemed to join together to form a network. If the cells and branches are of an oligodendroglial nature it is apparent from their staining reactions that they are not

fully developed oligodendroglia. They may belong to an incompletely differentiated stage. Other observers have not found such branches in oligodendrogliomas, except by using special staining methods. But in these loosely formed ventricular tumours the amount of fibre formation is likely to be greater, and certainly the opportunities for observing the fibres are infinitely better, than in the usual oligodendroglioma with densely packed cells. The network is seen in this case, partly because it is unusually stainable and partly because the conditions are unusually favourable for displaying it.

Of the greatest theoretical interest also is the presence of a small nodule of growth in the scalp. I know of no established instance of tumours arising from cerebral tissue growing outside the central nervous system. In the clinical account of one of the cases of oligodendroglioma described by Bailey and Bucy it was stated that the patient when last heard of "seemed to be developing an extra-cranial extension in the neck." That was eight years after his first operation and more than a year after his fourth operation. This had not been verified anatomically, but the writers thought the observation sufficiently reliable to comment on it. There are, therefore, now these two cases which suggest that oligodendroglioma cells may have the power of propagating when implanted in a mesodermal tissue.

If this nodule was oligodendroglioma, we must suppose that it arose from tumour cells which were sown in this situation at the time of the operation, twelve and a half months before the patient's death. In that case it had taken more than a year to form a spherical mass one centimetre in diameter—a fact which indicates in a new way the slowness of growth of oligodendroglioma.

Remarks on the Clinical Features and on the Life-History of Oligodendrogliomas.

Clinical records of four cases and some clinical features of nine other cases were given by Bailey and Bucy. Carnegie Dixon and Jumentié and Thomas also gave clinical descriptions of their cases. These accounts are easily available to English readers and need not be detailed. Among older records there are the cases described by Landau [6] and by Ziveri [11]. The tumour in Landau's case was composed of small glial cells having deeply staining nuclei and only an indefinite rim of cytoplasm; the margin of the tumour was characterized by an increase in the small glial elements and the satellites of the nerve cells; there

were calcareous deposits in the growth. The patient was a man aged 29, who, three and a quarter years before his death, had had a few epileptiform fits. He then had bouts of headaches at long intervals. Up to the time of his death he presented no abnormal neurological signs with the exception of tremor in his left arm for a few weeks before he died. The optic discs were normal. At the autopsy the right frontal lobe was found greatly enlarged by tumour and by œdema.

Ziveri's patient began to suffer from fits about the age of 37, and died five years later in an asylum. He became blind and deaf and had epitileptiform attacks at intervals of two or three months. He made no complaint of headache and had no vomiting. There was no loss of power in the limbs and no changes in the reflexes. Shortly before his death the patient had paralysis of voluntary conjugate movement of the eyes to the left, slight bilateral exophthalmos and bilateral anosmia. The tumour occupied the right prefrontal lobe and the anterior part of the temporal lobe. The cells composing it were small and of uniform size; their nuclei were rich in chromatin but their cytoplasm stained only faintly and with difficulty. In the margin of the growth there were "numerous granular cells evidently derived from the third element." In the histological description there is no mention of calcification.

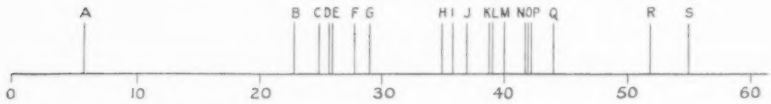
With the two cases described here there are in all nineteen clinical accounts on which we can draw.

In sixteen cases the tumour lay laterally in the cerebral hemispheres in a situation where it did not interfere directly with the circulation of the cerebrospinal fluid. Evidently oligodendrogliomas have a tendency to lie in the frontal and parietal lobes, for only one of these sixteen tumours was temporal and one occipital.

In three cases the tumour lay across the middle line of the brain—in one (Carnegie Dixon) [4] in the floor of the third ventricle, in another (André-Thomas and Jumentié) [1] passing across from one lateral ventricle to the other, and in the third (Bailey and Bucy's Case 3) [2] growing in the septum lucidum. These three cases separate themselves sharply in their clinical features from the others. Their symptoms began at an earlier age, the course was much shorter, there was no calcification in the tumours and the results of operation were unfavourable. These cases must be considered atypical. In central situations the nature of the growth has little opportunity to influence the clinical course, and the clinical condition is dominated by the features of hydrocephalus. Consequently these three cases will

not help us towards the clinical recognition of cases of oligodendroglioma, and we need give them relatively little consideration.

AGE OF THE PATIENTS.



	Age	Case		Age	Case
A	6	Carnegie Dickson.	K	39	B. and B. Case 4.
B	23	André-Thomas and Jumentié.	L	39	B. and B. Case H. C. G.
C	25	Bailey and Buey. Case 3.	M	40	Martin. Case 2.
D	26	Landau.	N	42	B. and B. Case 1.
E	26	B. and B. Case P. E. M.	O	42	B. and B. Case 2.
F	28	B. and B. Case 6.	P	42	B. and B. Case 7.
G	29	B. and B. Case Hans G.	Q	44	B. and B. Case 9.
H	35	Martin. Case 1.	R	52	B. and B. Case 8.
I	36	B. and B. Case 10.	S	55	B. and B. Case Mary D'A.
J	37	Ziveri.			

The marks on the accompanying diagram indicate the ages of the patients at the time of the onset of their symptoms, and it is at once clear that oligodendrogliomas are tumours of the middle third of life. In 84 per cent. of the cases (16 of 19) symptoms began between the ages of 23 and 45.

Of the sixteen tumours which lay in the cerebral hemispheres away from the middle line, none produced symptoms till after twenty-five, and the average age at the onset was 38. Two tumours did not manifest themselves until the patients were over 50, and it is worthy of note that these were both situated in "silent areas" in the right cerebral hemisphere. All the others began to cause symptoms during the age-period 25 to 45.

The three tumours which lay in the middle line produced symptoms before the age of 25, the average age of the patients at the onset of symptoms being 18.

If we consider the age of the patients by the time they came to operation, we find that in the tumours of the "hemisphere" group the average was 43, with extremes at 33 and 56; in the "mid-line" group the average was 18, the extremes being 6 and 25.

In both the cases recorded here the patients had had symptoms for three years before severe signs of intracranial pressure came on and in other cases of the "hemisphere" group described by Bailey and Bucy, intervals of ten, eleven, and even seventeen years have elapsed before increasing intracranial pressure rendered operation necessary.

The average period which intervened between the first symptom and operation (or death) in the sixteen cases in which the tumour lay clear of the middle line, works out at four years and nine months, the maximum being seventeen years and the minimum eight months. Even neglecting the extreme case in which the interval was seventeen years, the average was nearly four years.

Little need be said in regard to the actual symptoms since these depend more on the situation of the tumour than on its nature, but the quality of the symptoms call for comment.

Severe paralytic phenomena were conspicuously absent throughout the whole series of cases. Even in two of Cushing's cases in which the tumour involved the pre-central gyrus, weakness of the face and slight aphasia were the only symptoms of defect. In one case, where the tumour was occipital, homonymous hemianopia was found on examination about ten years after symptoms had begun, and in my second case slight unsteadiness in the right arm and leg were associated with a large parietal tumour. But with these exceptions "deficiency" symptoms of any severity were absent from all the fully recorded cases. This fact prompts the thought that the growing oligodendroglioma compared with other gliomas must cause little destruction of the brain tissue of the host.

On the other hand, "irritative" phenomena were frequent. Generalized convulsions were one of the earliest symptoms in five out of the eight cases of "hemisphere" tumours of which a history is available, and visual Jacksonian attacks were for ten years the only symptom in a sixth case (Bailey and Bucy, Case 12). Motor Jacksonian attacks seem to have occurred in one case only, and in that instance twitching was confined to the right side of the face and neck. Petit mal attacks occurred in two cases. Several of the patients were treated for years as cases of epilepsy.

Headaches seem to have been the first symptom in about one-third of the cases of hemisphere tumours. In my first patient the pressure of the cerebrospinal fluid two years after the onset of the headaches was found to be only 145 mm. of fluid, so that headaches can hardly be attributed to increase of the general intracranial pressure. Local displacement of cerebral structures from occasional swelling of the tumour must be held a more likely cause. In conjunction with this view the fact that the tumour was degenerated must be borne in mind, and it is doubtful whether any of these tumours caused symptoms until degeneration had occurred in them.

Long periods of complete remission of the symptoms were a feature of several cases. In the third year of his illness my first patient had a period of nine months in which he had not even a headache, and this freedom extended up to within a few weeks of the outburst of intense signs of intracranial pressure. Landau referred to two similar remissions in his case, and other instances are found in Bailey and Bucy's Cases 1 and 4. These remissions also must be correlated with physical changes in the tumours associated with degeneration.

The feature most likely to bring the possibility of an oligodendroglioma into consideration in a case of cerebral tumour is the X-ray appearance. With modern radiological technique calcification within the tumour has been visible in the films in all the cases of oligodendroglioma of this "hemisphere" or "lateral" group. In the three cases of mid-line tumours no calcified shadows were seen.

The chief feature in a good film is an irregular stippling, coalescing in places to produce wavy streaks or a moniliform appearance. Isolated flecks of calcareous deposit may also be seen and in the stereoscopic picture a mass of the tumour may be faintly indicated by an opalescent appearance, although one cannot say that any definite calcareous shadow is present in it. The deposits are in the central part of a mass of which the limits are vague. For the detection of the calcified deposits the quality of the X-ray films is of the greatest importance. This is emphasized by the experience of my first case in which they were recognized eleven months later, not because they had materially increased but because the films were much better. In two of Cushing's cases examined before the introduction of the Potter-Bucky diaphragm no calcareous shadow was seen.

Calcification in intracranial tumours is not very uncommon. The subject has been studied by Van Dessel [10], who reviewed the cases radiographed at Cushing's clinic in the years 1921-1925. Among 126 cerebral gliomas, there were seventeen (13 per cent.) in which some calcification was visible. The shadows fell into three types. Most common were irregular streaks; in a few cases there were curved lines suggesting that the deposit lay in the wall of a cyst; while the third type, of which there was only one instance, was "massive." The first type of shadow was shown by thirteen tumours (10 per cent.) and four of these were oligodendrogliomas, the remainder being astrocytomas and neuroblastomas. Differential diagnosis of the nature of the tumour by means of the shadow is not possible because the calcareous deposits lie chiefly in the walls of the arteries and capillaries.

Calcification takes place presumably during the latter years of the tumour's life. The oligodendrogliomas which have been described at the earliest stages (mid-line tumours) showed no calcification although they were already large and partly degenerated. The age of the host is almost certainly an important factor in this process, for Hurst [5] found in a great variety of other cerebral conditions that calcification was rare before the age of 30. The oligodendroglioma which lies across the middle line of the brain causes hydrocephalus and brings about the death of its host before either tumour or host is of sufficient age for calcification to occur.

The colour of the tumour when seen at operation in my cases was dark red with a blue tinge; when removed and cut the tissue appeared lighter—"pinkish-blue" or "light plum" coloured. Bailey and Bucy described the tumour in one of their cases as "reddish gray." Bailey and Cushing [3] commented on this point as follows: "They are tumours of peculiar appearance, sometimes showing a pinkish colour on fresh section, and they could hardly be mistaken for any other lesion unless possibly for a neuroblastoma." Carnegie Dixon [4] described the colour after fixation as "pinkish brown." The large necrotic centre of hæmorrhagic colour with a "cortex" of "fleshy" consistence may also help in the recognition of these growths.

Microscopical examination of the margin of the growths shows that they do not infiltrate at all widely and that a few millimetres away from the edge of the tumour the brain tissue is apparently healthy (fig. 7). But the tumours encountered at operation are large masses of irregular outline, and it would be impossible to remove every particle of the tumour and of the transition zone, however narrow, unless one removed at the same time a wide margin of healthy brain. They are, however, relatively favourable for palliative operation, and the primary results obtained have been excellent.

Having regard to the long pre-operative phase and the immediate results of operation, the post-operative period in my cases was somewhat disappointing. The first patient remained well for more than a year and then died with symptoms which indicated an extension of the tumour in the inferior part of the left frontal lobe. The second patient was re-admitted to hospital within nine months of his operation with a recurrence of his former symptoms and died four months later.

The fact that the average interval between the occurrence of the first symptom and the time of operation was nearly five years demon-

strates that oligodendrogliomas, at any rate, when they lie in the cerebral hemispheres, are tumours of slow growth. Moreover, calcification is the expression of an extremely chronic degenerative process, and all the "hemisphere" tumours which have been described were already partly calcified by the time they were discovered.

The supposition that many of these tumours have been present for a very long time before their discovery, is supported also by the great difference in the age at which symptoms appeared according to the situation of the growth relative to the channels of the cerebrospinal fluid. The mid-line tumours because of their obstruction of the cerebral fluid circulation caused symptoms early; they gave evidence of their presence at the average age of 18. But the tumours in the cerebral hemispheres did not manifest themselves till the average age of 38—a difference of twenty years. Neglecting the quite exceptional case of Carnegie Dixon, the difference between the average ages at operation in the two groups is eighteen and a half years. The suggestion is that if one of these growths lies in such a position that it does not readily obstruct the cerebrospinal fluid circulation, it goes on, before compelling operation, for eighteen and a half years longer than if it is so situated as to cause obstruction early. While this last argument may not apply without modification to all cases, e.g., to my Case 2, these various considerations do nevertheless suggest that the life of the tumour is so long that the beginnings of pathological growth are in most instances to be referred to the early adult life of the host.

Summary.

(1) Two cases of oligodendroglioma are described. The first corresponded closely with previously recorded cases, but the second ran a more malignant course and pathologically showed a number of extraordinary features. Small masses of growth were found throughout the ventricles, and the cells in these ventricular growths showed branches. A nodule of growth was also found in the scalp in the base of the operation flap.

(2) The clinical features of these and the previously-recorded cases are reviewed. The cases divide themselves sharply into two groups, according to whether the tumours lay in the cerebral hemispheres away from the middle line, or whether they lay across the middle line, thus interfering with the circulation of the cerebrospinal fluid at an early age.

(3) The former group consists of sixteen cases; in them symptoms began on the average when the patient was 38, the extreme ages being

25 and 55; in seven-eighths of the cases symptoms began during the age period 25 to 45; severe paralytic symptoms were conspicuously absent, and "irritative" symptoms were frequent; operation was not called for on the average until four and three-quarter years after the onset of the symptoms; in both the cases recorded here the interval before operation was three years; absolute remission of symptoms for nine to twelve months was a feature of several cases; calcification visible by the X-rays has been present in all the cases of this group examined by modern X-ray methods. At operation, the growth in both my cases was visible on the surface of the brain, and showed an unusual bluish-red colour. The primary operative results in nearly all the cases were excellent. Recurrence of symptoms has occurred, however, in my cases thirteen months and nine months after operation, and both the patients have died.

(4) The "mid-line" group consists of three cases: in them symptoms appeared much earlier—before the age of 25, the average age being 18, with extremes of 6 and 23, the pre-operative period was short (3 to 9 months), no calcification was present in the tumours, the results of operation were unfavourable.

(5) The site of election of oligodendrogliomas is in the frontal and parietal lobes. In many instances the tumour probably begins to grow in early adult life. The nature of the symptoms to which it gives rise prompts the suggestion that during growth it does not cause much destruction of cerebral tissue. The "hemisphere" tumour becomes lightly calcified during the latter part of its life, but the "mid-line" tumour compels operation or causes death too early for deposits of calcium to occur in it.

I wish to express my thanks to Dr. Hinds Howell for allowing me to study and record Case 2, and to Dr. J. G. Greenfield, for his constant help in the pathological examination of the tumours, and for the photographs.

Addendum.

Although, as has been said, no other cases of oligodendroglioma were found in the National Hospital records of the last ten years, it happened that while this paper was awaiting publication three cases of this kind, and most probably a fourth, were admitted to the hospital within a few weeks. They conformed closely to the description that has been given.

In the first case the tumour was in the left frontal lobe. The patient

was a man of 44 who had been subject to occasional fits for fifteen years; he had had periods of freedom from symptoms lasting several years; headaches had been troublesome for the past year and the right leg had become slightly weak. In the X-ray picture there were heavy flecks and streaks of calcification. Nearly all the tumour was removed by operation and the patient made an excellent recovery.

In the second case also the tumour was in the left frontal lobe. The patient was a man, aged 38, who for about a year had been getting mentally inert and complained of general loss of energy. No fits had occurred. He had signs of high intracranial pressure but no paralysis. The X-ray films showed an indistinct stippled shadow of calcification above the left orbital plate. The tumour found at operation was a very large one, and its removal was followed by a fatal result a few days later. In connection with this case it may be observed that in general the history of symptoms is shorter if no "irritative" symptoms occur.

In the third case the nature of the tumour was not confirmed histologically, but its other features seem to warrant its inclusion here. The patient was a man, aged 33, who had had fits off and on for three and a half years, and recently had had occasional severe headaches, with vomiting, and slight weakness of the right face and hand. The X-ray pictures showed calcified deposits scattered throughout a volume as large as a cricket ball occupying the site of the left pre-central and post-central gyri and their underlying white matter. A better demonstration could hardly be given of the scarcity of defect symptoms in association with these tumours. Removal of the growth was obviously inadvisable and only decompression was done. The tumour was seen presenting on the surface of the brain and it had the bluish-red colour seen in cases of oligodendroglioma.

The fourth case belonged to the "mid-line" group. The tumour filled the posterior part of the third ventricle and sent a tongue down into the aqueduct of Sylvius. The patient was a girl, aged 16, and the clinical features were those of hydrocephalus. The patient had always had a large head, but symptoms had only been present for ten to twelve months. Death occurred twenty-four hours after ventriculography. There was no calcification in this tumour.

I am indebted to Dr. Collier, Dr. Adie and Dr. Grainger Stewart for permission to refer to these cases, and again to Dr. Greenfield.

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CUTANEOUS TACTILE LOCALIZATION.

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I.—The Supposed Pathway for Cutaneous Localization.

Normal persons are able to localize the site of cutaneous stimulation with a degree of accuracy which varies with the part of the body surface stimulated. This faculty has been investigated by many workers, including v. Frey, Head, and more recently Stopford, and the current ideas with regard to the mechanism which underlies it embrace a detailed scheme of peripheral and central pathways. Definite localization fibres in the peripheral nerves, connected with end-organs which respond to any form of stimulation in their immediate vicinity, are supposed to pass into the spinal cord where they continue upwards towards the brain in a tract distinct from that of cutaneous discrimination. In the brain-stem the impulses subserving tactile localization are supposed to become separated off from the associated tactile impulses and, after passing through the thalamus, to have cortical representation.

Localization is regarded as belonging to the epicritic group of sensibilities. It is held that after section of a peripheral nerve localization with the rest of this epicritic group is lost over a greater area, and is recovered later, than is the group of protopathic forms of sensibility. The pattern of the sensory impairment resulting from this dissociated loss of the "cruder" and of the "higher" forms of sensibility after nerve section is explained upon a purely peripheral factor—a difference in the distribution of the cutaneous fibres subserving the protopathic and epicritic forms respectively. Attempts have been made to

account for the changing conditions found during the process of nerve regeneration in terms of a difference in the rate of recovery of nerve fibres concerned with these two supposedly different types of sensibility. A difference in their rates of growth, for example, has been postulated by Ranson, but Stopford considers that the evidence in favour of this explanation is insufficient [22, p. 374], and refers us to the other end of the hypothetical localization pathway, to the cerebral cortex, for the elucidation of this problem.

Thus the considerations invoked to explain the delay in the return of the ability to localize cutaneous stimuli and those invoked to explain the wider loss are totally different, but an attempt is made to soften this disparity by the reflection that "on general grounds it seems only reasonable to expect to find an explanation of the two stages of recovery in the cerebral hemisphere, and such a view has the added attraction of illustrating once again that the functions of the nervous system are integrated on the principle of evolution" [Stopford, 22, p. 378]. The inconsistency of this step is masked by the observation that it involves a "sound physiological principle" [Stopford, 22, p. 377], since "ultimately we must of necessity turn to the sensory cerebral centres for any explanation of the changes in consciousness induced by various stimuli" [Stopford, 22, p. 377].

Apart from other implications of the protopathic and epicritic hypothesis, this view of the nature of cutaneous localization entails the following suppositions which, for reasons about to be given, must be considered to be invalid.

There must be a specific end-organ which responds to a specific attribute of the stimulus applied—its position on the body surface (its "immediate vicinity"). It is difficult enough to imagine the essential character of a purely painful stimulus apart from mechanical, thermal or chemical agencies; it is a form of stimulus which can be defined only in terms of the sensation which its application evokes. A localization stimulus in the same sense is a verbal fiction.

The fibres which are activated by the "site" of the stimulus convey to the cerebral cortex impulses which are there interpreted as local signs; interruption of their messages allows the recognition in the cortex of sensations of touch, heat, &c., but without any accurate indication of the whereabouts of their peripheral origin. Stimulation of these fibres and tracts ought therefore to lead to a sensation of "there-ness" without any conception as to what is happening "there." Now although in certain cases of diminished cutaneous sensibility a person may be able to localize

with accuracy a stimulus without being able correctly to describe its nature, yet the stimulus appears to be of some definite form particularized by the subject of this sensory examination. He will say, "I cannot be sure as to what it is but it feels as though. . . ." something or other were happening. In other words, a sense of localization divorced from any sense of quality does not occur, and it would not be expected to occur because we can no more conceive of a sense of "site of stimulation" apart from a stimulating object than we can conceive of the idea of space as a pure representation apart from any impression.

Yet the fact remains that given an adequate stimulus there is produced in the consciousness of any normal person a twofold sensation corresponding to the nature of the stimulus and to its point of application, the recognition of quality and of localization, an impression and a judgment, and some more acceptable view of the factors underlying this judgment is required.

II.—The Localization of Touch.

Although touch has received more than current mention in nearly all works dealing with sensation, the only definition or description is given by Trotter and Davies [25]. These authors describe the sensation of being touched as that of receiving a superficial "minute pat" within a small, well-defined area; it never feels heavy and is accurately localizable [25, p. 158]. They also agree with v. Frey [10, p. 95], who pointed out that the sensation arises at the moment when contact of a suitable agent with the skin is made and again when it is interrupted. The sensation of touch, whenever evoked, has invariably the same characteristics; thus, in areas of diminished but recovering sensibility, touches, although elicited only by a heavy bristle which pits the skin, resemble the same superficial pat within a small but well-defined area [25, p. 158]. An important characteristic of this same form of sensibility is lack of quantitative variation. With true touch, "if the stimulus fails to produce a perfectly distinct, fully-developed sensation it is not felt at all [25, p. 158]. Although changes in other stimuli may produce variations in the intensity of the other sensations aroused, "no such continuous series of intensities can be produced for touch" [25, p. 158].

The sense of touch has in this and in other ways to be sharply differentiated from the sense of pressure. Both may be originated by mechanical stimuli applied to the skin without affecting the subcutaneous structures [25, p. 222], but it is held that they "cannot be

regarded as forming a continuous series with the sole distinction of degree in the force of the stimulus," but are subserved by independent "physical and physiological mechanisms." Pressure, besides its sense of "heaviness," increases with perseveration of the stimulus alone and gives rise to only a "vague idea of extent or locality" [Trotter, 25, p. 158].

Upon the observations of touch in areas of normal, hypoæsthetic and recovering sensibility have been based various theories in regard to the nature of this sensation. Trotter and Davies have laid it down that any theory to be acceptable must provide an adequate explanation for tactile hypoæsthesia, and it is in this respect that many fall short of the requirements. To remedy this defect these authors have themselves made the following suggestions as to the essential nature of the tactile mechanism. Touch and pressure sensations are both responses to mechanical deformation of the skin, but each is subserved by an independent physical and physiological mechanism. The essence of the stimulus giving rise to touch is movement, that of the stimulus giving rise to pressure is compression, i.e., the essence of the touch stimulus is rate of change, reflected in its dependence upon its time relations, that of pressure is "static contact."

Since the conceptions of "change" and "maintained alteration" are so fundamental to the distinction between touch and pressure, it is worth while pointing out that the word "contact" used in this context is apt to give rise to confusion. When two objects have contact each with the other they may be supposed to be in a condition of contiguous juxtaposition, i.e., in common parlance, "just touching." There is no suggestion as to any forces normal to the surfaces of contact, i.e., no pressure or deforming force exerted between them. In this sense, the only difference between "moving contact" and "static contact" would be one of duration only, the former occurring instantaneously and the latter for a varying period. In so far as an object applied to the skin, if it is to evoke a sensation either of touch or of pressure, must bring about some local deformation, however slight, its relation to the *surface* may be that of contact, but its relation to the *body* must be that of a deforming force. It is not the contact as such, but the slight deformation which sets up the impulses giving rise to the sensation of touch. It seems probable that in an attempt to provide additional emphasis for the most important distinction between touch and pressure, Trotter and Davies have strained contrast unduly, for their observations have led them to "expect to find in the physical mechanism of touch means

whereby *movement* is very directly transformed into a nervous impulse" [22, p. 218]. It is inconceivable that movement, as such, should be transformed into nervous impulses apart from any secondary effects of movement such as resulting tensions or compressions within the body. Even if, as they suggest, it is the movement of a hair-bulb away from the surface which initiates the nervous impulses, the argument still applies, because the body would take no account of movement of the hair-bulb apart from resulting forces exerted upon structures within it (the hair-bulb) or without it, any more than it would of the passage of a bullet or a knife through the tissues apart from the compression and tearing effects produced. Moving contact and static contact are perhaps unhappily chosen terms for these characteristics, but the difference which underlies them is clear and more definite than the obscurity of the phrase "the contact of tactile pressure" [Stopford. 21, p. 407] would lead one expect.

In view of these considerations, it appears that mobility alone, whether of the skin or of the hair-bulb, cannot determine the sensitivity of the surface. In addition to this difficulty in regarding the touch stimulus as differing in quality from the pressure stimulus, there are other reasons for disbelief in a specific tactile mechanism in the skin. Thus, although the cornea of the eye has been usually held to give rise only to pain sensations as the result of any adequate stimulus, Goldscheider and Bruckner [12] have found that a sense of contact, although obscured in most subjects by pain, can be perceived by some and can be in others unmasked by cocainizing the cornea lightly.

Although the neighbourhood of the hair-bulbs is especially sensitive to light touches, these can also be felt when a stimulus is applied remote from the hairs and even on areas unprovided with hair. Therefore, there is evidence to show that a sensation of touch may be elicited by very light stimulation of a structure, such as a naked nerve-ending, which with degrees of stimulation usually encountered during life give rise to pain. The above observations on the sensitivity of the cornea support this view, and simpler animals respond to very light stimuli such as give rise in man to the sensation of touch (although no inference can reasonably be drawn as to sensation in them) from surfaces where the cutaneous receptors are limited to free nerve-endings or to a very few pacinian corpuscles [15, p. 73]. Moreover, Adrian has shown [3, p. 49] that in the frog and in the cat free nerve-endings can give rise on light stimulation to a brief outburst of impulses characteristic of touch, and on slightly stronger stimulation to a continuous, prolonged stream of

impulses characteristic of pressure or of pain. In the cases where, using a mechanical stimulus, impact produces touch and pain impulses, and pressure produces pain impulses only, Adrian brings forward evidence to show that the stronger stimulus does not activate additional end-organs but stimulates the same end-organs to a further degree. The lightest effective touch produces an outburst of impulses lasting for a fifth of a second only. This is due to rapid adaptation of the receptive structure or end-organ. Pain discharges in the peripheral nerve are characteristically prolonged and probably give rise to the appropriate effective response in the central nervous system by virtue of this extended duration which provides successive summation at some central synapse.

Therefore there is good reason to believe, (1) that although in the neighbourhood of the hair-bulbs the conditions are especially favourable for the initiation of a disturbance interpreted centrally as touch, yet they provide only local intensification of a responsiveness which is more widespread, and (2) that the difference between the types of discharge underlying touch and other forms of cutaneous sensibility is one of degree only.

The characteristics of the touch which is derived from the normally innervated skin are shared by that which reappears with regeneration of a previously divided peripheral nerve. Authorities differ as to the form in which touch reappears. The explanation of this discrepancy in results lies probably both in the method of testing and in the subjective analysis of the sensation aroused. But the fact of significance which stands out and as to which all authors agree, is that as soon as such a stimulus becomes adequate, the sensation elicited, whether that of true touch or of pain, is endowed with a local sign. Even when associated with pain, this local sign is sufficiently well marked for Schäfer to note both local and peripheral reference, and when associated with touch it is so emphatic that Trotter and Davies comment upon the surprising precision with which the part involved may be described. Thus, tactile stimuli, as soon as they become adequate, give rise to a sensation having local signature associated with an impression determined by the method of examination and standards of reference used.

III.—The Relation between Touch and Localization.

The sense of touch has been shown by Trotter and Davies to be a well-established and distinct form of sensibility having certain well-recognized characteristics, distinguishing it from all other forms of

sensibility, including pressure. It has also been argued in the previous section that there are no adequate grounds for regarding the peripheral mechanisms of touch and pressure as being distinct. The peripheral nervous mechanisms appear to be identical, the sensations aroused are subjectively very different. It may well be asked what it is that endows the sense of touch with a character so sharply distinct from that of pressure.

The peculiarities of the touch sensation, which cannot be ascribed to a special peripheral mechanism, must depend upon some peculiarity of the central response. The characteristic of the central response or sensation is the association with the impression (of touch) of a judgment (localization). The view which it is the purpose of this paper to advance, is that the function of what is generally called the sense of touch is localization; accurate localization apart from touch does not exist as a sensory impression, but only as a theoretical concept. It is maintained that an examination of the characteristics of the sense of touch shows that it is indissolubly linked with that localization, and that no other function than this can reasonably be ascribed to it.

Trotter and Davies have drawn attention to the unnaturalness of the sensation of touch as derived from experimental observations "when we remember how rare in ordinary life is any practice in the discrimination of slight touches passively received" [25, p. 142]. v. Frey states that in this sense (of touch) a light pressure is never or only under special circumstances a *transitory* sensation [10, p. 95]. Yet since the sensation of touch is a reality when sufficient care is given to its recognition, and since also all "sensation has developed in man to keep him precisely informed as to the nature of his customary environment" [25, p. 142], there must be some significance in its existence.

v. Frey has pointed out [10, p. 95] that our body surface is constantly subjected to mechanical changes which are of much greater degree than those which are used to elicit the sensation of touch. The pressure of air and of water from outside, and the tension changes produced by the blood-vessels and the pull of connective tissues do not normally enter consciousness because the stimulus is simultaneously applied over a wide area; such changes are appreciated immediately they are localized ["ortlich begrenzte," 10, p. 95]. Generalized pressure evokes no sensation; localized pressure evokes a sensation, not because the quality of the impression is different, but because it is associated with a local sign.

The particular stimulus used to elicit the sensation of touch is never

appreciated unless localized in its application. The significant characteristic of the stimulus of touch lies in its restriction in extent, i.e., its localization. The significant characteristic of the sensation aroused by this stimulus is the recognition of this restriction, i.e., of its localization.

Thus, the characteristic stimulus provided by a minimal local deformity of the body surface sets up a very brief neuronic discharge leading to fugitive sensation in which two factors, a judgment and an impression, are mingled. The former, the recognition of the site of stimulation, has been shown to stand out with surprising emphasis. The latter only reveals itself upon careful introspection. It is here suggested that the former element is the significant one, and that the latter element has become grafted on to it as the artificial product of sensory examination with an " unnatural " stimulus.

If this view is correct, it follows that the characteristics of the form of sensibility known as light touch should be shared by the faculty of localization, i.e., accurate localization of cutaneous stimulation should be possible when the sensibility to touch is present and in abeyance when this form of sensibility is absent. Further, localization should share with sensibility to touch its independence of variations in the stimulus strength, i.e., it should not show a graded variability with changes in the stimulus, and hypoæsthesia in respect of localization should consist in a higher threshold value for stimuli capable of arousing a localizable sensation but not in the less accurate localization of a given stimulus.

It should be noted that it is not here implied that localization of all peripheral stimulation is provided by the mechanism of light tactile sensibility alone. Probably all adequate stimuli, whatever their nature, initiate a centripetal afferent discharge which bears some form of local signature, but it *is* suggested that it is only when the form of stimulation involves mechanical deformation of the skin that localization is accurate.

A series of three experiments was devised with a view to testing the inferences drawn from this hypothesis. In the first two the relation between the accuracy of cutaneous localization and stimulus-strength was investigated. In the last the accuracy of localization of stimuli involving mechanical deformation of the skin was compared with that of stimuli free from such deforming effects.

Experiment 1.—The error of localization of stimuli delivered with a graded series of v. Frey hairs was measured. The sensibility of the dorsum of the

hand and fingers was examined and an apparatus was used to lower the hair on to the skin at a uniform and constant rate. Hairs varying from 50 to 4,000 mgm. bending-pressure were prepared, and of these four were selected having maximum bending-pressures of 120, 225, 450, 1,440 mgm. Ten stimulations were made with each hair and the errors of localization averaged in each case. It was found that for the ten normal persons examined, out of ten stimuli delivered with the 120 mgm. hair, on an average four were not appreciated at all. The results are summarized in the following table :—

TABLE I.

Subject	Hair 120	Hair 225	Hair 450	Hair 1,440
F.	4·5	4·5	7·0	5·0
C.P.	3·4	3·5	5·3	4·1
S.	6·5	5·2	5·4	4·7
N.P.	5·1	6·7	5·5	5·2
S.T.	5·7	5·8	7·6	4·5
L.B.	7·2	5·8	6·4	5·5
A.K.	4·3	4·0	6·2	5·0
N.	3·4	4·6	4·6	4·1
C.L.	3·7	5.6	4·8	4·9
P.L.	6·0	5·3	7·2	6·2
Average ..	5·0	5·1	6·0 *	4·9

* The fact that this figure is so much higher than the other average values is probably due to a defect in method : it is interpreted as due to the fact that each subject examined was stimulated with this series (450 mgm. hair) of stimulations first before the lighter and less easily appreciated hairs were used, i.e., the subjects were less "trained" in the method of the experiment than for the other hairs.

From this table it will be seen that although with weaker hairs several stimuli were not recognized, the error of localization of the stimuli appreciated was not reduced by increasing the stimulus-strength. (See Appendix, p. 366).

Table I giving the error of localization, measured in centimetres, shown by each of ten normal persons when stimulated with four v. Frey hairs of varying strengths—measured in milligrams of maximal bending-pressure.

Experiment 2.—In another subject the neighbourhood of the ulnar nerve at the elbow was infiltrated with novocain solution. Anæsthesia of the ulnar border of the hand and fingers developed within half an hour and persisted unaltered for three and a half hours. It passed off progressively during the following hour and a half. The localization of cutaneous stimuli was tested before injection, during maximal anæsthesia and repeatedly during the recovery phase. In the photographs, fig. 1, two areas are shown. The smaller area is that over which no stimulation of any kind was felt; the larger area is that over which stimuli, if felt at all, were less distinct than over normal areas.

Over the area where sensibility was present but subjectively diminished, the lighter v. Frey hairs were not appreciated and the heavier occasionally missed. Yet the localization of those stimulations which were appreciated was of the usual order of accuracy.

During the phase of returning sensibility successive stages were reached at which stimuli of progressively lighter hairs began to be appreciated. Records of the localization errors at each stage show that as soon as a stimulation of a given strength began to be appreciated at all it was localized with the customary accuracy. (See Appendix, p. 366.)

A B

FIG. 1.—Subject S. T.

A. Time 1.10 p.m., i.e., 50 min. after ulnar infiltration with novocain.
Motor weakness: Paresis of all small hand muscles; adduction of fingers imperfect; opposition of thumb weak.
Sensory loss (shown in photograph):—
Area to ulnar side of the continuous line completely insensitive to all forms of stimulation.
Area between continuous and broken lines showed subjective diminution of appreciation of brush and pin-prick stimulation.

B. Time 4.50 p.m., i.e., 4 hours 30 min. after ulnar infiltration.
Motor disturbance shown only by slight weakness of adduction of thumb.
Sensory loss: Over area to ulnar side of dotted line pin-prick felt but not sharp; over area between dotted and interrupted lines pin-prick felt as sharp but light touch subjectively impaired.

Experiment 3.—The dorsal surface of the hand and fingers was stimulated by approaching a source of heat at various points. The skin was not touched

but the nearness of approach and the duration of the stimulation were adjusted so that a distinct feeling of warmth was appreciated in the neighbourhood of the stimulus. The error of localization of the point maximally warmed in this way was measured in the same way as was used for the recording and measurement of tactile stimulations. The error of localization of such stimulations is shown in Table II.

TABLE II.

Subject	Average error of localization of ten stimuli
F.	12 mm.
C.P.	9 ,,
S.	8 ,,
B.P.	10 ,,
S.T.	6 ,,
L.B.	12 ,,
A.K.	15 ,,
N.	9·5 ,,
C.L.	10 ,,
P.L.	13 ,,

From these results it can be seen that the error of localization of this form of stimulus, not involving any mechanical deformity of the skin, is much greater than the error of localization of tactile stimulations. (See Appendix, p. 366.)

From these three experiments it is inferred that:—

(1) Accurate localization is present whenever sensibility to touch is present and is absent when sensibility to touch is absent. Also the characteristics recognized as belonging to touch are shared by localization.

(2) Stimuli which do not mechanically stimulate the skin, i.e., do not touch, are not accurately localized.

But this view, that sensibility to touch is inseparable from the faculty of localization, is not generally held. It is currently believed that responses to touch can be obtained without localization, both in lower animals and in man.

The existence in the lower animals of protopathic or dyscritic touch endowed with no local sign is a figment of scientific theory. The observations of Piéron [16], Parker [14], and others go to show that the responses which are initiated in the lower forms of life are always appropriately directed and that accuracy of localization is essential to the value of the response.

When we turn for comparison to the responses evoked by tactile stimulation in organisms at the other end of the scale of complexity, man, we find that accuracy of localization is their chief characteristic.

For not only do tactile stimuli yield precisely localized responses, whether associated, as in normal conditions, with what is described as the sense of touch or, as in conditions of recovering sensibility, with a variety of other qualities of impression, but tactile stimuli divorced from local application (not "ortlich begrenzte") are not appreciated at all.

Tactile responses in their earliest appearance, at a stage when the element of impression or qualitative aspect of sensation, as we know it, cannot reasonably be supposed to have existed, were characterized by accuracy of localization. Tactile responses in creatures of most advanced neural development are still characterized essentially by accuracy of localization.

A presure stimulus when sharply limited in extent evokes a judgment of locality. Since this locality is upon the body surface and attention is always normally attracted to it by a stimulus from outside the body, this judgment of locality is exteriorized. Now all sensations have become mentally integrated into perceptions, and these perceptions are exteriorized into the objects to which we refer as our surroundings. In the same way local signature, when presented to us by carefully controlled experiments which rob it of those impressions which in ordinary life invariably accompany it, is exteriorized and secondarily linked up with an impression (which is the re-presented product of our introspection) to form a perception, our idea of what the stimulus must have been like to have been presented to consciousness in that form.[1]

When our visual localization mechanism is abnormally stimulated the same thing happens. When a focus of irritation along the course of the visual apparatus from the retina to the occipital cortex leads to pathological stimulation, visual hallucinations are aroused. When the visual cortex itself is thus abnormally stimulated these tend to be of a gross, unorganized form; flashes of light, sheets of coloured cloud, &c. When the optic tracts are irritated and the visual cortex is intact, these hallucinations are frequently much more elaborate and highly organized.

[1] Schäfer's experiment [19, p. 195] of placing a block of ice upon the skin overlying the ulnar nerve in his arm provides a neat illustration of this linkage of local signs due to minimal stimulation with a qualitative impression which is normally foreign to the stimulus used. He found that if the cold employed was sufficient to stimulate the fibres of the nerve below the skin, "there would be experienced a peripheral reference of sensation of an indeterminate character caused by stimulation of all the fibres of the nerve trunk to which the cold is applied." The peripheral reference was unequivocal; the sensory quality with which it was linked was indeterminate. The simultaneous activation of nerve fibres which were distributed peripherally over a wide area and which were normally never subjected to simultaneous but to successive stimulation must have provided a central disturbance with no parallel in normal experience and therefore difficult of description because unfamiliar to perception.

Things or persons are seen in certain positions and moving about in particular directions. Never does such a patient complain that his attention becomes riveted upon or drawn towards a particular direction without having any impression as to an object present or to an event occurring in that direction.

IV.—The Physiological Significance of Tactile Localization.

The capacity for localization has been shown to be intimately associated with (and it has been suggested that it provides) that form of cutaneous sensibility known as the sense of touch. Clearly the provision of this sense of touch cannot be regarded as being in any way the natural rôle of the faculty of localization. The real function of localization is that of adjusting and directing the movements which arise in response to stimulation.

Reflection shows that the sense of touch and the adjustment of motor responses are more intimately related than may be immediately obvious. For the sense of touch leads man to elaborate his perception of tactile space, and this allows him to inter-relate the relative positions of the objects around him. This perception of the spacial disposition of surrounding objects enables him to move with accuracy and safety among them. This is recognized by Parsons, who has pointed out that the essential biological function of space perception is control of movement [15, p. 146], so that these two derivatives of localization are direct and indirect views of the same thing. It is because of the characteristic exteriorization of mechanically aroused impressions that we develop tactile space perception.

A mechanical stimulus of the order of touch evokes an impression together with a local sign which leads to its being exteriorized; the more insistent the local sign the more complete is this exteriorization The sensations of heat, and cold and pain are never projected in the same degree. Perhaps it is because we are so familiar with the pain which arises from sources within our body surface that we can more readily conceive of "having a pain," or even of a part of our body being "painful" without the presence of an external causative agent, than we can of being touched or pressed upon without the presence of something external to ourselves exerting a force upon us. We become hot and cold too readily in response to change in the temperature of the air about us, or to our own exertions or sluggishness, to infer always the presence of an external source or drain of heat, and even when

radiated heat is confined to a comparatively small area of our body surface we are not able to localize the stimulus with accuracy.

In the simplest of those animals which do not invariably move as a whole, but which have one or more parts of their body specially adapted for mobility upon the rest, movements are directional and adjusted with a degree of accuracy which, did we imagine them to be capable of the conscious appreciation of a sensation, would argue a developed sense of localization. Such movements of primitive animals are responses to direct stimulation; in man voluntary movements are responses, not so much to direct stimulation as to the represented images evoked by the stimulus, and are therefore directed more by that previous experience from which the perceptual content of consciousness has been built up. This is why the conception of space appears at first sight to be distinct from the control of movement.

Also in normal persons, the significance of tactile space perception is overshadowed by that of visual space perception: for sight is in this way complementary to touch, and with its aid tactile space perception achieves a scope and a significance which it could not otherwise acquire. But touch and vision have more in common than the dual provision of space perception. We have seen that the local signature of touch provides accurately directed responses of relatively mobile parts of the body at a low phylogenetic level. In the most primitive photosensitive organisms the appreciation of light is a tropism which directs the movements not of one part of the body with reference to the rest, but of the whole body in relation to its surroundings. There have thus been two parallel lines of development; that of touch which has passed from the stage of purely segmental adjustment to that of egocentric localization,[1] and that of vision which has passed from the stage of a simple photosensitive tropism to that of spacial orientation.

These parallel lines of development have taken place because both touch and vision possess another common characteristic, not merely by association but as a result of their very nature. Both are completely exteriorized. Both have to be defined objectively and not subjectively. In this, as we have seen, they stand in the sharpest contrast with pain which has to be defined subjectively and not objectively. Visual impressions are not more completely, but only more distantly exteriorized than tactile impressions, and vision leads to a representation, as far as

[1] "Ontogenetically, touch builds up the egocentric self which is the point of reference," for "so-called absolute, better egocentric localization depends on reference to the body" (Parsons [15], p. 153).

space perception is concerned, of the same relations as does touch, but through a mechanism capable of greater precision and elaboration. When we see an object we do not merely associate visual and tactile impressions, we exteriorize and identify both in the object.

Through whichever avenue it is received, localization is not a pure impression but a judgment, and the sense data of space perception which it provides become significant under comparison only. For a local sign, if it is to provide an absolute measure in itself, must be distinct from a certain part of the body surface or of the retina, even if always associated with it, otherwise it would simply be another name for "position" and not indicative of position: it would *be* position and not *signify* position. Similarly, comparison, or differences of quantitative, qualitative or motor impressions may *become* signs of external spacial relations, although not original signs provided by "space." Such differences can become signs of external spacial relations by association only, and this presupposes previous experience of their significance through some other source. Thus, comparison of simultaneous and successive visual impressions provides the means for more delicate and elaborate space perception as a result of association with the material of tactile space perception. That this correlation between visual and tactile space perceptions has to be learnt is shown, as Parsons has pointed out [15, p. 156], by those cases of cataract in which patients blind since birth have acquired vision after a successful operation comparatively late in life. We cannot assume that ideas of space may be presented alone as a pure representation apart from the impressions which accompanied the original local signs, for consciousness is built up out of impressions, not of judgments. It has been pointed out that we never have a sensation of "there-ness," or locality of stimulation, apart from an impression (accurate or inaccurate) of the kind of event which is happening "there." So also we cannot conceive of "a space" as an absolute thing apart from its material boundaries, i.e., apart from impressions. We can think of "the space within A" or of "the space between B and C," but we think in terms of the distance apart of the containing walls of A, or of the distance which separates B from C. This is why the conception of "space infinite" or limitless space, stretching indefinitely, defies the imagination, and this phrase remains an association of words without significance; imagination stretches out for ever after that further wall within which to conceive of space.

Just as the three-dimensional space of vision is built up from the

simultaneous association of perceptions of distance (which is one dimensional), so is the conception of "distance-apart" of touch built up from the simultaneous association of tactile local signs, and a distance-apart is conceived of as the spacial separation of two simultaneously stimulated points (which have position but are non-dimensional).

But the mobility of our eyes and of our limbs, through the sensations aroused as the result of proprioceptive impulses received from the muscles providing this movement, enables us to adopt a more active rôle than is assumed in the above passive reception of stimuli, and to the results of *simultaneous* association are added those of *successive* association. Simultaneous association alone would only enable us to appreciate and compare surface areas by vision and linear separations by touch. Successive association enables us to conceive of three-dimensional space through both vision and touch. Simultaneity of touches, each purely qualitative and each providing an independent sense datum, is the passive element of the synthesis from which space perception is ultimately derived through the agency of movement and the accompanying proprioceptive impressions. When a succession of touches in a certain order accompany a movement, their local signature and the proprioceptive impulses consequent upon the movement automatically transform "succession" into "space." Thus the sense of touch or of localization, originating in passive reception as the controlling element in adjusted movement, comes to co-operate with movement and to be in its turn directed and applied through movement, as an active instrument for the provision of space perception.

Thus it appears that not only is tactile space perception necessary for the co-ordination and adjustment of our movements, but only accuracy in the execution and assessment of our movements makes the development of tactile space perception possible. Each is essential to the other and both are ultimately derived from a common physiological basis—the mechanism of cutaneous localization.

Summary.

(1) The current view of the mechanism underlying the localization of cutaneous stimulation is described and discussed.

(2) The mechanism of cutaneous tactile sensibility suggested by Trotter and Davies is described and criticized.

(3) The view is advanced that the function of what is usually referred to as the sensation of touch is the provision of localization.

(4) A series of experiments have been made in order to test the implications of this hypothesis. It is claimed that these experiments show that:—

(i) Accurate localization of cutaneous stimulation is possible when the sensibility to touch is present and is in abeyance when this form of sensibility is absent.

(ii) Localization shares with sensibility to touch its independence of variations in the stimulus strength.

(iii) It is only when the application of the stimulus used involves mechanical deformation of the skin that accurate localization is possible.

(5) Tactile responses of the simplest, as well as of the most complex animals are characterized by accuracy of localization.

(6) The physiological significance of tactile localization is discussed and its co-operation with proprioceptive judgments for the provision of space perception is outlined.

Appendix.

Experiment I.—In this experiment measurement was made of the error in localization of the site of stimulation with v. Frey hairs of varying strength.

The calibration of the v. Frey hairs.—The hairs were calibrated in terms of the maximal pressure which the bent hair could exert upon the pan of a balance. Each hair was held vertical over the balance pan and lowered until it just touched. The graduated rider-chain was set in a position equivalent to a weight of 2 mgm. in the other pan of the balance and the beam was released. The vertical height of the hair was then adjusted so that the pan was pressing upwards against the hair with this pressure of 2 mgm. without perceptibly bending it, and the pointer of the balance was over the zero of the scale The other pan of the balance was then progressively loaded. The hair bent slightly more under each increase of the load until a value was reached at which it yielded and bent suddenly. The maximum load which was supported before the break occurred was taken to be the maximum bending-force of the hair. The balance used was kindly lent by Dr. C. R. Harington, of University College Hospital Medical School, and was of the "chainomatic" type, so that the load could be continuously varied over a range of 100 mgm. without any sudden increase. The

final value was reached in all cases with an approximation of less than 10 mgm.

The method of testing.—For comparison of the error of localization of successive stimuli it is necessary that as the stimulating hair is moved from place to place, the only factor changed should be the spot pressed upon, i.e., the rate at which the pressure is applied must be constant and the hair free from lateral movement. The manual application of the hairs was found not to give sufficiently constant stimulations, so that the apparatus shown in fig. 2 was devised to ensure this.

The lever "A," pivoted at the point "F," is tipped slowly in an anti-clockwise sense by a weight "W" in the piston of the dashpot "D." The other end of the lever carries a small wheel which pushes up the near end of the lever "*a*" pivoted at "*f*" against the downward pull of the weight "*w*." This rotates the lever "*a*" in a clockwise sense and

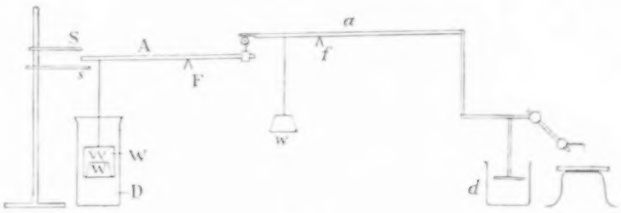

FIG. 2.

lowers the far end, to which the v. Frey hair is attached, with a steady uniform motion. The arm of the lever "*a*" carrying the hair is made as long as is convenient in order to give a motion to the hair as nearly vertical as possible. A second dashpot "*d*" is provided to free the lever "*a*" from those vibrations to which its great length makes it liable. The support which attaches the hair to the lever "*a*" is provided with a universal joint so that the hair can be readily adjusted over any point of a wide area.

The subject tested sits with his arm fully supported so that his hand lies beneath the hair, but in such a position that the apparatus and his hand are shielded from his view. He is provided with a photograph of an extended hand which he is required to prick at points exactly corresponding to the points on his own hand which he imagines to have been touched. On a rough diagram he also indicates the approximate positions of these points by means of numbers, 1 to 10 corresponding to the ten stimuli applied. The person testing the sensibility is provided

TABLE III.

		1	2	3	4	5	6	7	8	9	10	Average error
Subject F.	Hair 120	0	10	5	7	2	3	–	—	—	—	4·5
	,, 225	0	6	7	8	4	3·5	3	5	4	–	4·5
	,, 450	0	0	8	3	3	14	11	17	—	—	7·0
	,, 1,440	0	6	4	8	2	8	7	9	2	4	5·0
Subject C.P. ..	,, 120	0	3	8	2·5	—	—	—	—	—	—	3·4
	,, 225	0	0	0	5	8	8	4	—	—	—	3·5
	,, 450	0	0	7	5	11	4	6	8	7	—	5·3
	,, 1,440	0	2	14	4	12	8·5	8	10	4·5	8	4·1
Subject S.	,, 120	0	21	4	6	4	4	—	—	—	—	6·5
	,, 225	0	0	9	8	8	7	6	3	5	—	5·2
	,, 450	0	0	0	6	3	11	11	12	—	—	5·4
	,, 1,440	0	0	0	4	16	4	5	6	4	8	4·7
Subject B.P. ..	,, 120	0	6	3	4	7	11	—	—	—	—	5·1
	,, 225	8	9	9	7	5	2	—	—	—	—	6·7
	,, 450	0	4	7	6·5	10	14	4	3	4	3	5·5
	,, 1,440	0	0	0	12	9	4	9	6	4	8	5·2
Subject S.T. ..	,, 120	2.5	4·5	4·5	3	14	—	—	—	—	—	5·7
	,, 225	0	0	10	15	4	—	—	—	—	—	5·8
	,, 450	0	2	14	14	12	4	8	11	3·5	—	7·6
	,, 1,440	0	0	9	3	3	11	10	2	3·5	4	4·5
Subject L.B. ..	,, 120	12	4	8	4	12	6	4	—	—	—	7·2
	,, 225	0	9	4	11	6	3·5	8	6	5	—	5·8
	,, 450	0	0	8	4	12	12	6	4·5	10	8	6·4
	,, 1,440	0	0	7	2·5	3	10	12	8	7	5	5·5
Subject A.K. ..	,, 120	0	7	6	2·5	6	—	—	—	—	—	4·3
	,, 225	2	4	9	3·5	4	5	2·5	2	—	—	4·0
	,, 450	0	0	7	11	3	12	10	8	6	6	6·2
	,, 1,440	0	0	2	3	7	9	8	9	2	10	5·0
Subject N.	,, 120	0	2·5	6	3·5	7	—	—	—	—	—	3·4
	,, 225	0	0	8	12	6	2	5	4.5	—	—	4·6
	,, 450	0	3	6	6	10	4	6	3	4	4	4·6
	,, 1,440	0	0	0	9	4	8	8	3	6	3	4·1
Subject C.L. ..	,, 120	4	2·5	2·5	7	3	5	2	—	—	—	3·7
	,, 225	10	5	6	6	8	4	4	7	6	—	5·6
	,, 450	0	0	0	4	5	9	10	12	4	4	4·8
	,, 1,440	0	0	7	4	9	4	9	3	8	5	4·9
Subject P.L. ..	,, 120	0	8	4	10	9	5	—	—	—	—	6·0
	,, 225	0	0	6	3·5	5	5	4	14	10	6	5·3
	,, 450	0	11	8	12	10	7	6	4	8	6	7·2
	,, 1,440	0	0	4	6	9	9	5	10	12	7	6·2

Table showing the error in localization of stimulation over the dorsum of the hand and fingers in ten subjects, each tested with ten stimulations with each of four v. Frey hairs. The four hairs are distinguished by the different maximal bending-pressures: 120, 225, 450 and 1,440 mgm. The localization errors are recorded in millimetres:—

0 = no measurable error of localization.

— = stimulus not appreciated at all.

with a similar photograph and diagram—he pricks the photograph and numbers the diagram at the points over which he then adjusts the hair. He releases the free end of the rod "A" from the support "S" from which it falls as far as the stop "*s*." The hair is thereby lowered until it rests, fully bent, upon the skin.

The two photographs are then compared and the pricks on one are transferred to the other; the distances between corresponding pricks (determined by the numbering of the diagrams) are measured in millimetres to give the error of localization of each stimulation.

Table III gives the error of localization of ten successive stimuli delivered with each of a series of four hairs of different bending strengths.

Experiment 2.—It was decided to examine the error of localization over an area in a condition of tactile hypoæsthesia. For this purpose some means was sought of providing such an area quickly and transitorily so that the localization could be tested while the skin sensibility was normal, when it had been made hypæsthetic and after it had again become normal.

TABLE IV.—SUBJECT S.T.

Time	Hair	1	2	3	4	5	6	7	8	9	10	Average
11-11.45 a.m. ..	120	2·5	4·5	4·5	3	14	—	—	—	—	—	5·7
..	225	0	0	10	15	4	—	—	—	—	—	5·8
..	450	0	2	14	14	12	4	8	11	3·5	—	7·6
..	1,440	0	0	9	3	3	11	10	2	3·5	4	4·5
12.20 p.m. ..	Ulnar infiltration with 1·5 c.c. novocain (2 per cent. solution with adrenalin) at elbow.											
1.30 ,, ..	1,440	0	15	7	3	8	3	—	—	—	—	6
1.50 ,, ..	225	0	0	4	9	10	3·5	4	8	—	—	4·8
2.15 ,, ..	120	7	4	11	4	2·5	5	—	—	—	—	5·5
4.15 ,, ..	1,440	0	10	7	3	6	4	4	—	—	—	5
4.25 ,, ..	450	0	5	3	5	—	—	—	—	—	—	4·3
4.35 ,, ..	225	4	8	5	2·5	7	10	—	—	—	—	6
4·45 ,, ..	120	0	0	3	4	10	7	5	—	—	—	4·1

v. Frey hairs distinguished by maximal bending-pressures in milligrams.
Errors of localization with ten successive stimulations given in millimetres.
0 = no measurable error of localization.
— = stimulation not appreciated at all.

An attempt was made to adopt the means used by Stopford, which consisted in treating an area of skin with a 10 per cent. solution of cocain hydrochloride in chloroform. But a saturated solution, which was of less than 5 per cent. strength, gave no detectable hypoæsthesia

after repeated tests. Therefore the cocain alkaloid, which is much more readily soluble in chloroform, was used as a 10 per cent. solution. Repeated painting of the same area of skin resulted in no detectable diminution of sensibility.

A patient whose arms were in every way normal was therefore chosen, and an infiltration of 2 per cent. novocain solution with adrenalin (in water) was made just behind the median epicondyle around the ulnar nerve. Cutaneous sensibility over the fifth finger and part of the fourth finger and of the hand rapidly showed signs of diminution; subjectively within ten minutes and to objective testing within twenty minutes. By forty-five minutes the sensory impairment was maximal and its extent is shown in fig. 1, p. 359. The error of localization of stimulation with a v. Frey hair was measured before the injection was made, while the sensory impairment remained maximal and repeatedly as it was wearing off. The results are shown in Table IV.

Experiment 3.—An attempt has been made to compare the error of localization of stimulation with some form of stimulus not involving any mechanical contact with the skin, with that of tactile stimulation. Heat seemed the only form of stimulus fulfilling this requirement, and some means had to be found of supplying heat to a sharply localized area of the skin. No convenient means suggested itself for focusing a distant source of heat on to different parts of the skin in reasonably rapid succession; although such a means would be ideal for the purpose.

TABLE V.

Subject	1	2	3	4	5	6	7	8	9	10	Average
F.	14	11	24	15	9	4	8	4	12	7	12
C.P... ..	20	7	16	7	4	8	5	6	13	6	9
S.	4	8	12	3	10	15	9	9	7	4	8
B.P. ..	9	5	15	18	10	17	11	8	4	6	10
S.T. ..	0	0	8	4	12	4	10	5	10	11	6
L.B. ..	0	15	10	10	15	3	25	15	20	—	12
A.K. ..	17	9	11	18	15	25	12	4	16	23	15
N.	0	15	8	7	9	11	3	14	8	20	9·5
C.L. ..	3	5	9	11	32	10	9	10	8	6	10
P.L. ..	12	15	8	16	12	20	5	9	20	14	13

Table giving errors of localization shown by ten subjects, each tested with radiated heat stimulation.
Errors measured in millimetres.
0 = no measurable error of localization.
— = stimulation not appreciated at all.

The most practicable source of heat was found to be supplied by a piece of platinum wire sealed in glass in such a way that only a small loop was left bare at one point. The wire was heated by the passage of an electric current so that the exposed loop became red-hot. The heat from other parts of the wire was taken up by the glass to some extent, and this was kept cool by some damp asbestos fibre wrapped round it. The free ends of the platinum loop were connected through a vulcanite holder to leads from the accumulators.

The stimulus was applied by approaching the glowing loop, by hand, to within about 1 mm. of the skin and withdrawing it at once. The error of localization was measured in the same way as for touch on similar photographs and diagrams and the results are given in Table V.

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Notices of Recent Publications.

The Evolution of the Nervous System in Invertebrates, Vertebrates and Man. By C. U. Ariëns Kappers. Haarlem: Bohn. 1929. Pp. 335. Price 8.75 florins.

In his preface the author states that the purpose of his book is to give a general survey of the nervous system and to make his readers acquainted with its chief evolutionary principles, and no better description of its scope and use can be suggested. Starting with the nervous system of the invertebrates, which is dealt with only in sufficient detail to allow the reader to grasp the broad principles on which it is constructed, he gradually leads him through the lower vertebrate series to the primate brain, and finally, in a series of most interesting chapters, discusses the anthropology of the human brain, its characters in prehistoric man, and describes the chief morphological features of the brain in living races.

This treatment of the subject will appeal to the anthropologist, and indeed to all interested in the natural history of man, as well as to the student of medicine and neurology, and the simple and lucid presentation of the subject, the wealth of illustrations which supplement the descriptions, and finally the readable style in which the book has appeared, should ensure its popularity. It is not, however, merely a popular treatise thrown on the market to catch the eye of the casual reader. The author's eminence in this subject and his rigidly critical review of facts places it in a wholly different category. Anyone reading it through carefully will, for example, acquire a completer knowledge of the comparative anatomy of the vertebrate nervous system than he can obtain from any similar source, and will learn more of the mode of development of the cortex and basal ganglia than is easily available elsewhere.

For the anatomist this smaller volume cannot replace the author's now classical work on the comparative anatomy of the nervous system, but it deserves the attention of every neurologist, and especially of anthropologists who attempt to base observations and conclusions on scientific principles.

Anatomie du système nerveux. Par Paul Cossa. Paris: Amédée Legrand. 1931. Pp. 400. Price 60 francs.

It is natural to expect that a textbook written by an anatomist acquainted with the needs of clinical investigation should be simpler and more useful to the student at least than the work of an academic anatomist who describes structures regardless of their clinical significance. Dr. Cossa is a clinician and has produced such a book suitable to the undergraduate student entering on a study of neurology. The main divisions of the nervous system are first described, and in the final chapters the chief systems of conduction tracts are

dealt with separately. There are numerous illustrations, all simple drawings and many of them diagrams, on the whole adequate but rather crudely executed.

In view of its purpose it is naturally dogmatic and raises no doubts on many of the unsettled problems on which it touches, but unfortunately there are no references to which the reader can turn for further information, and few authorities are cited in support of statements made. The fact that French rather than Latin titles are given to most of the structures limits its value to English students.

Diagnostic des tumeurs cérébrales et épreuve de l'encéphalographie artérielle. Par EGAS MONIZ. Paris: Masson et Cie. 1931. Pp. 512. Price 100 francs.

The first third of this volume is devoted to a description and discussion of the symptoms of tumours of the brain, the remaining chapters to the use in diagnosis and localization of the method of arterial encephalography introduced by the author. This, as is now generally known, consists in the injection of a soluble substance opaque to X-rays into the internal carotid artery and the immediate exposure of a film in which the course of the larger cerebral vessels can be then seen. Sodium iodide is recommended in a 25 per cent. solution, and the author claims that if the precautions he advises are followed the injection entails little risk and few unpleasant complications. Fatal results followed immediately on injection in only two of his cases, both in patients with advanced arterial disease. The presence of a tumour can be recognized either by the presence of abnormal blood-vessels within it, or by the displacement of the arteries from their normal course.

There may be difficulties in the interpretation of the films, but these are fully discussed. The author's own experiences are illustrated by numerous figures which will be useful to others who wish to employ his method. Its value cannot be determined till independent observations are available, but Professor Monix, in this excellently written book, has at least furnished an interesting contribution to the literature of cerebral tumours.

Die Allgemeinerscheinungen der Hirngeschwülste. Von F. KEHRER. Leipzig: Georg Thieme. 1931. S. 116. Price M. 10.50.

This book contains two main chapters. In the first the ordinary and well-known signs and symptoms of cerebral tumours—as headaches, vertigo, vomiting, papillœdema, epileptiform attacks and psychical changes—are dealt with, and though little new is added to our knowledge the analysis and the discussions on the origin of some of those symptoms are undoubtedly important, as they are often accepted without question of their nature.

The second chapter bears the title of "A Group of New General Symptoms"; these include "Pain Reflexes" and "Pain Reactions," excited by mechanical stimulation of a nerve or of tissues in the peripheral distribution of a nerve. One

striking feature of this sensitiveness of the tissues is that the patient is not conscious or aware of it. It is, therefore, an objective sign and is regarded by the author as evidence of irritability of protopathic sensation, and probably directly due to the increase of intracranial pressure. The importance claimed for these pain reactions is that they may make it possible to recognize the existence of a tumour before the classical signs of pressure appear, and in certain cases they may help in its localization.

The various "new signs" described by Kehrer must be studied in his book and controlled by independent clinical observations; till this is done their significance and importance cannot be determined. The book is certainly worth reading.

La myotonie atrophique; sa place entre la maladie de Thomsen et les myopathies. Par LUCIEN ROUQUÈS. Paris: Amédée Legrand. 1931. Pp. 229.

This excellent review of the clinical and pathological features of myotonia atrophica deserves the attention of all physicians interested in the muscular atrophies and in the hereditary diseases of the neuromuscular system. The clinical symptoms are fully described from the author's own observations and a review of the literature of this disease and of the related myopathies and myotonia congenita and their significance and relationships are discussed critically. Dr. Roquès had the opportunity of making a complete pathological study of one case only; this revealed no important differences from the eight cases in which autopsies had been already published, but it enabled him to re-examine certain points of interest and correlate the available pathological findings. A very extensive bibliography adds to the value of the volume.

The Commoner Nervous Diseases. By F. J. NATTRAS. Oxford University Press. London: H. Milford. 1931. Pp. 218. Price 12s. 6d.

This small book on the commoner diseases of the nervous system supplies a definite want in English medicine. It has been written chiefly for the general practitioner, but should also prove useful as an introduction to neurology for students.

The first chapter is an admirable exposition of the principles of diagnosis; it is illustrated by a series of diagrams and photographs, and written so clearly and concisely that even the least experienced can readily follow the routine of examination recommended by the author. Little reference is made to either the anatomy or the physiology of those parts of the nervous system involved by disease in explanation of the symptoms, and pathological anatomy and pathogenesis are in most cases neglected, but these scarcely come within the scope of the author's aim in producing this volume. The diseases and pathological conditions most commonly met with in practice are dealt with in separate chapters, considerable attention being given to their treatment.

Ueber Heilungsmechanismen in der Schizophrenie. Von MAX MÜLLER. S. 143. Berlin: S. Karger. 1930.

Regarding schizophrenia as an organic process characterized by onto- and phylo-genetic regression, Dr. Müller sets about the analysis of those reparative processes which spontaneously or in response to external influences tend towards restoration of the normal state of affective contact with the environment and adaptation to reality. He even includes as related mechanisms those in which the diffuse schizophrenic primary experiences are dominated or disposed of by higher psychic processes, and worked upon by logical thinking in the direction of systematized delusions. He uses mainly the phenomena observed during remissions, as well as descriptions of their experiences by the patients themselves.

The first part is concerned with the affective relations to the environment, especially as manifested towards the physician and in daily occupation. From the elaboration of psychotic experiences by intellectual and dynamic tendencies, the author passes to an inquiry into the formation of false beliefs, whether associated with insight or not, and the patient's subsequent refusal or inability to recapitulate the happenings of the acute illness. From his investigations, based on a rather small number of cases, the author is led to see opportunities of therapeutic intervention, but the indications are of the most general kind. Throughout the book there is evidence of wide and critical reading rather than of original thought or observation.

Frühsymptome geistiger Erkrankungen. von ERNST WITTERMANN. S. 32. Leipzig: Fischer. Price M.1.

This brochure is designed for the general practitioner, who is expected in Germany to have a rather fuller acquaintance with modern psychiatry than is usual in this country. The familiar early symptoms of mental disorder are set forth clearly and simply, with references to the work of Kretschmer, Gruhle and other recent writers. The organic reactions are dealt with best.

Ritual: Psycho-analytic Studies. By THEODOR REIK. With an Introduction by Sigmund Freud. Pp. 367. London: Hogarth Press. 1930. Price 21s.

This book has received the best of ancillary care; it is admirably translated and admirably set up. As a psycho-analytic study of the presuppositions and aims of religion it has much intrinsic value, and Dr. Reik explicitly repudiates any claim that his method is suitable for dealing with all the aspects of religious phenomena.

In a moderate and clear introduction he gives his reasons for selecting ritual still in use as the starting-point for an examination of religious problems.

The first section deals with couvade, which he regards as a landmark in cultural development, indicating the suppression of a fear of retaliation in favour of the more kindly and self-denying parental affections. The puberty rites of savages are then discussed with much learning and acuteness. The origins of the Kol Nidre renunciatory prayer are considered, and the strain of guilt running through all these ceremonies is related to primitive patricide. Finally, Dr. Reik offers an interpretation of the ritual significance of the ram's horn, with a discussion on the beginning of music and a supplement on the Moses of Michael Angelo (already treated by Freud) and the events on Sinai. To ethnologists who are prepared to accept psycho-analytic assumptions and methods of approach, this study will prove informative and stimulating; the more conservative will see in it daring conjecture, having the merit only of inner consistency.

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EDITOR.